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AN AID FOR THE DIAGNOSIS OF CONDITIONS ASSOCIATED WITH AN OBSTRUCTION TO THE OUTFLOW OF BLOOD FROM THE BRAIN; WITH SPECIAL REFERENCE TO SINUS THROMBOSIS OF OTITIC ORIGIN.*

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The two main pathways by which the venous blood is returned from the brain are formed by the symmetrically placed lateral sinuses, jugular bulbs, and internal jugular veins.

The main channels for a collateral circulation in case of obstruction to the outflow of blood through either of these main pathways are:

1. Through the superior and inferior petrosal sinuses to the cavernous sinus.
2. From the cavernous sinus:
   (a) To the facial vein through:
      (1) Supraorbital vein.
      (2) Superior and inferior ophthalmic veins.
   (b) To vessels of the scalp through numerous emissary veins and the sinus spheno-parietalis.
   (c) To the cavernous sinus on the opposite side by way of the sinus circularis.
3. Through the occipital sinus and posterior emissary vessels to the vertebral plexus and the external posterior jugular vein.

Thus it may be seen that there are two systems for the venous circulation in the head—one intracranial and one extracranial. These two systems are united by means of numerous anastomotic vessels; and in case there is sufficient obstruction to the outflow of blood through the intracranial system, these anastomotic vessels will become engorged with blood. At least two of these vessels, the supraorbital and ophthalmic veins, can be seen on the surface of the skin. On the other hand the retinal veins are the only branches of the intracranial venous system which can be directly observed. These vessels, however, may be studied very conveniently with the aid of an electric ophthalmoscope.

Stasis in the intracranial venous system, as may be produced by compressing both internal jugular veins, will immediately manifest itself by a dilatation of the veins of the fundi. As the stasis increases the anastomotic vessels will also begin to dilate. If the pressure on the right jugular vein is suddenly released, but that on the left is still maintained,

[1] I am indebted to Dr. Oscar Beck, assistant in the K. K. Universitäts-Ohrenklinik in Vienna, for the privilege of observing many of the cases mentioned in this paper. It was also through his kindness that the writer was permitted to assist in the operative procedures on these cases.

or vice versa, it will be observed that the distended veins in the fundi and in the skin immediately collapse and return to their normal size. This is to be explained by the fact that in normal individuals the connections between the two internal jugulars are so free, that one side alone may be occluded without producing any marked evidence of stasis. If it were otherwise one would expect to find evidence of stasis in the eye-grounds in every case of sinus thrombosis. But such is not the case. Ruttin,[2] for example, has recently reported 30 cases of sinus thrombosis in which the sinus was opened and the internal jugular vein ligated; in only 8, however, was there any evidence of choked disc. Although in 6 of these cases the choked disc did not make its appearance until after the ligation of the jugular, still there remain 22 cases in which the ligation of this vein did not produce a choked disc. We are inclined then to agree with Wagener[3] that the choked disc in cases with a sinus thrombosis is probably due to a meningitis serosa, or some other cause rather than a direct stasis of blood.

Our experience, then, has led us to conclude that any acute obstruction to the outflow of blood through the sigmoid sinus, jugular bulb or internal jugular vein on one side may be diagnosed by means of the following test. This test is based on purely mechanical principles. The anatomical conditions are schematically represented in the accompanying diagram.

From the examination of 50 normal individuals we have arrived at the following conclusions:

1. No appreciable evidence of stasis is seen in the retinal or supraorbital veins when *one internal jugular is compressed with the finger.*
2. *Pressure on both internal jugular veins at the same time* produces a marked dilatation of the veins of the fundi and of the anastomotic vessels connecting the intracranial with the extracranial venous circulation.
3. When *the pressure is suddenly released on one side, while it is maintained on the other,* the engorged veins of the anastomotic system and the fundi will immediately empty.

These are the three steps of the test which we wish to describe. If the results in any individual case differ markedly from those above, it must be concluded that there is either an anomaly of the intracranial venous circulation, or some pathological condition, which is obstructing the outflow of blood from the brain.

It is very important while making this examination that the patient should breathe freely and normally; that the collar should be loosened so as to expose the neck and upper part of the chest; and that the fundi should be examined by the direct method, or with an electric ophthalmoscope, while an assistant compresses the internal jugular veins with the tips of the fingers. The compression, however, should not be maintained longer than absolutely necessary for it may be possible in this way to rupture a diseased vein or dislodge a portion of a thrombus.

During the past two years we have had an opportunity of making this examination in 6 cases in which there was an acute obstruction, on one side, to the outflow of blood from the cranial chamber. In 5 of these cases the obstruction was due to a thrombosis, secondary to a chronic infection of the middle ear, and the test described above was employed in making the diagnosis. In 3 instances the first symptoms of the thrombosis appeared several days after the radical mastoid operation, and offered an excellent opportunity to determine the value of this sign. It is our custom to make this test before operation on all cases in which a sinus thrombosis is a possible or threatened complication. The examination of each of these 3 cases, before operation, indicated that the blood was passing freely into the internal jugular vein on both sides. This was also the opinion of the surgeon at the time of the operation, although in each case there was a cholesteatoma which extended backward to the dura of the posterior fossa. The wall of the sigmoid sinus and surrounding dura was thickened and covered with granulations. Before the operation, however, there had been no elevation of temperature, and the test had indicated that the blood was flowing freely into the internal jugular vein on both sides; therefore, it was deemed advisable to leave the sinus untouched and await developments. After a post-operative period of several days, free from discomfort or fever, the patient in each case began to complain of pain in the back of the head; there was a sudden elevation of temperature; a positive Kernig's sign; a low grade of choked disc; and some stiffness of the neck. After excluding angina, pneumonia and disturbances of the digestive tract it was necessary in each case to decide whether these symptoms were due to:

1. Serous meningitis with retention of pus in the operative wound.
2. Localized basilar meningitis.
3. Temporal lobe abscess.
4. Cerebellar abscess.
5. Sinus thrombosis.

On making the vascular test a second time it was found to be decidedly positive, *i. e.*, the stasis in the retinal and supraorbital veins was markedly increased by very slight pressure on the internal jugular vein on the healthy side, whereas at the previous examination the test had been decidedly negative. One could only conclude from this result that whatever other complications might be present, it was sure that the blood was no longer flowing freely into the internal jugular vein on the side of the operation. The sinus was immediately exposed and opened, and in each case found to be thrombosed.

In one of these cases, however, even at the second operation the sigmoid sinus was fairly normal in appearance, and on incising it there was a gush of blood. We were so sure, however, that there must be an obstruction somewhere between

[2] Ruttin: Ueber Stauungspapille bei otogenen Komplikationen. Verhandlungen der Deutschen otologischen Gesellschaft, Frankfurt-a-M., 1911.

[3] Wagener: Zur Kenntnis der intrakraniellen Komplikationen im Anschluss an Mittelohreiterungen. Passow-Schaefer Beiträge, 1911, IV, 205-256.

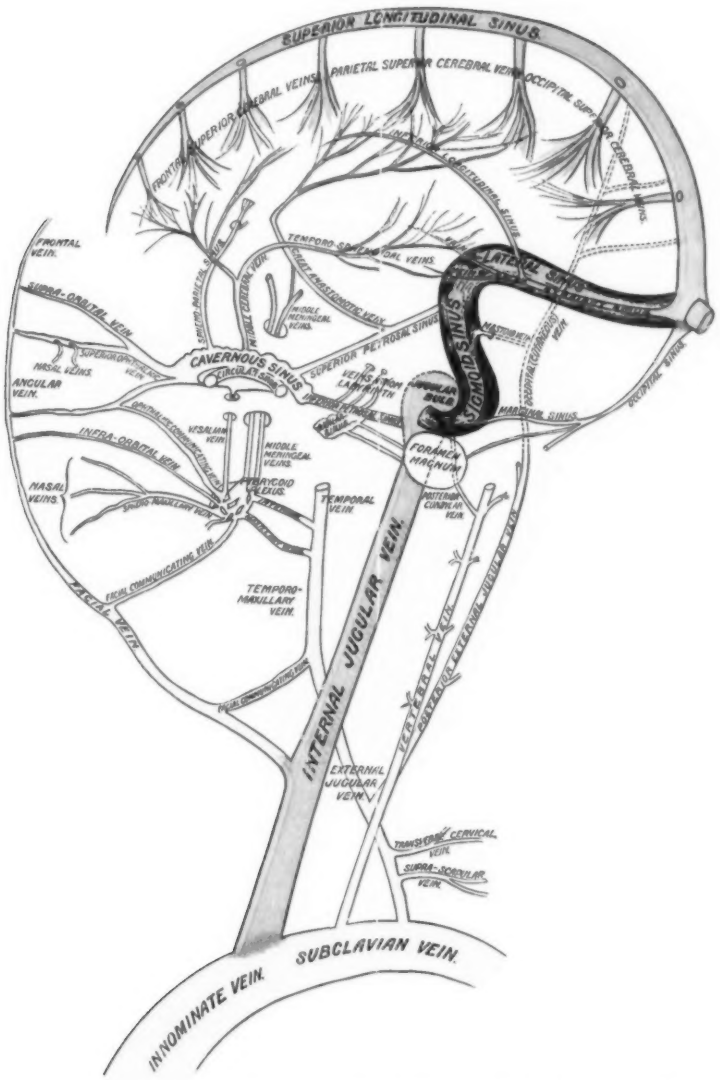

Fig. 1.—Diagram illustrating the intracranial and extracranial venous systems and their anastomotic vessels.

Blue = the intracranial venous system.
Brown = the extracranial venous system.
Red = the anastomotic vessels connecting the intracranial with the extracranial venous system.

(Modified from Macewen: Diseases of the Brain.)

this point and the innominate vein, that the cerebral end of the sinus was packed with gauze and the incision in the sinus wall enlarged downward. Then by pressure on the upper part of the internal jugular vein in the neck pus was forced upward into the wound. Further investigation disclosed a thrombus in the bulb which, however, was not purulent. Apparently this was a case of a primary abscess in the jugular fossa with a secondary thrombosis of the vessel. If we had not been certain, as a result of the positive test for stasis, that there was an obstruction to the outflow of blood into the jugular vein on this side, we should not have felt justified in opening an apparently normal sinus and exploring the bulb. Consequently the condition would not have been recognized until the peri-jugular abscess had become much larger and the chances for the patient's recovery less favorable.

The 2 remaining cases were not seen until after the operation, at which time the internal jugular vein had been ligated on one side. They are of value, however, since the test was positive in both instances, *i. e.*, light pressure on the internal jugular vein on the sound side immediately produced a dilatation of the retinal and supraorbital veins, which promptly disappeared when the pressure was released.

We have not been able to definitely determine the length of time this sign will persist after ligation of the internal jugular on one side. With this point in mind, however, we have examined 10 operated cases in which the sinus had been opened, and the internal jugular ligated, from six weeks to one year previously. In many of these cases compression of the jugular on the sound side produced no appreciable evidence of stasis, even in the retinal veins. It is our impression, therefore, that after a month or six weeks, the vessels for the collateral circulation become sufficiently large to compensate for the ligated jugular. One case, in which both sinuses had been opened and both internal jugulars ligated, by Dr. Ruttin, about fifteen months previously, was very interesting in this connection. In this man a tight bandage around the neck caused a flushing of the face, but no appreciable dilatation of the retinal veins, and but very slight subjective discomfort. This was apparently due to the fact that the collateral circulation was largely through the deep anastomotic connections with the extracranial venous system—the vertebral plexus, pterygoid plexus, etc. The fundi were also interesting. The outlines of the disc were not clear on either the temporal or the nasal side; the lamina cribrosa could not be seen on either side; and there were numerous areas of scar tissue on both retinæ, which probably represented the organization of large extravasations of blood.

Among the clinical conditions which may be associated with an obstruction to the outflow of blood from the brain, the formation of a thrombus in the sigmoid sinus, secondary to an infection of the middle ear, is by far the most frequent and the most important. Sinus thrombosis appears with equal frequency as a complication of acute and chronic cases of otitis media, and not infrequently the diagnosis offers great difficulty. Due to the anatomical position of the jugular bulb to the middle ear, it is possible to have a primary bulb thrombosis, with the sigmoid and transverse sinuses normal in appearance; and the condition may not be recognized, even at an exploratory operation. One of the cardinal symptoms of sinus thrombosis is a remittent fever with chills; due to the serious nature of the malady, however, it is desirable to know at an early stage of the disease whether the symptoms are really due to a sinus thrombosis, or to other conditions, such as: angina, pneumonia, malaria, the initial stage of one of the infectious diseases of children, meningitis or brain abscess.

As we have already stated, no normal person has as yet been observed by us in whom the compression of one jugular alone produced any marked degree of stasis in the retinal veins. On the other hand, in all normal individuals, a quite evident dilatation of these vessels results when simultaneous pressure is made on both sides of the neck. Since a sinus thrombosis offers a more or less complete obstruction to the outflow of blood into the internal jugular vein on the same side, it naturally follows that in such cases there will be unmistakable evidence of stasis as a result of compressing, with the finger, the internal jugular vein on the opposite side. When it is possible to examine a patient before the onset of complications and find that both jugular veins are patent, and at a later period, associated with an elevation of temperature, find that the blood is not passing down one side of the neck as freely as down the other, our observations have led us to believe that this sign may be taken as positive evidence that there is a sinus thrombosis.

CHLOROFORM POISONING.

RESISTANCE OF THE PIGEON, FROG AND TERRAPIN TO LATE CHLOROFORM POISONING.

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The comparative pathology of experimental chloroform poisoning offers many interesting points for investigation, and this field has not been carefully studied as yet. The few investigators (Ostertag and others) give very unsatisfactory reports of their experiments and in general state that the pathological lesions in the lower animals (birds, amphibia, etc.) are similar to the familiar lesions found in mammals. This report deals with the lesions of *late chloroform poisoning* and not the acute poisoning during anæsthesia. Particular attention was given to study of the liver. Recent publications

(Howland, Richards, Whipple, Sperry, Hurwitz) have reviewed the characteristic anatomical picture of delayed chloroform poisoning. The liver is the only organ which is seriously injured, and if the damage is severe the patient or animal dies from hepatic insufficiency. The hepatic lesion is studied to best advantage during the second day after the administration of the anæsthetic. In gross the central liver necrosis is very obvious at this time and the accompanying fatty degeneration may be conspicuous. The microscope shows a typical hyaline central necrosis of varying extent, in which areas the liver cells show pyknotic, fragmented or fading nuclei and hyaline necrotic protoplasm. The middle zone may show more or less fatty degeneration involving the liver cell protoplasm, and the marginal (portal) zone usually shows normal liver cells.

It has been shown conclusively that the common laboratory animals (dog, cat, rabbit, guinea pig, rat and mouse) react pretty constantly to chloroform anæsthesia. Two hours of surgical anæsthesia will almost certainly produce considerable central liver necrosis and fatty degeneration in these animals. The change is most conspicuous during the second day and, as a rule, this injury can be repaired rapidly and the liver brought back into a normal condition in a few days. If the injury is too severe, the symptoms become progressively more serious and the animal dies in three to five days with the familiar clinical picture.

It is also clearly established that human beings are similarly susceptible to chloroform anæsthesia, that fatal poisoning may follow less than one hour of anæsthesia and that the clinical and anatomical pictures are identical in every respect with those studied by animal experiments. It seems safe to conclude that mammals are pretty uniformly susceptible to late chloroform poisoning.

There is an interesting exception to this rule, however. In recent publications Whipple has pointed out the fact that fetuses in utero and pups during the first three weeks of life have a marked resistance to late chloroform poisoning. It seemed possible that this immunity might be explained by the "blood islands" or nests of blood-forming cells which are so conspicuous in the liver sinuses of fetuses and young pups. As these nests of nucleated red and white blood cells become less and less numerous with advancing age, one can detect a lessening of this peculiar resistance to chloroform poisoning. Surely there is a great temptation to correlate this protection of the liver cells against this poison (chloroform) with the presence of these nucleated blood cells. The mechanism of this protection is not clear.

Following this lead one might expect to find interesting differences in the reaction to chloroform anæsthesia on the part of animals with nucleated corpuscles. Below are reported the experiments in detail which go to show that in the case of the pigeon, frog and terrapin there is a very marked resistance on the part of the liver to the poisonous action of chloroform. This increased resistance is very obvious and easily established and this fact stands out clearly. Our explanation of this peculiar resistance may be quite wrong. However, it may be due to the presence of great amounts of nuclear material in the blood stream in contact with the liver-cell columns.

Chloroform, in its action upon the liver-cells, attacks the *nucleus* particularly, and the injured cell shows early nuclear degeneration or necrosis. This protective action, therefore, centers in the liver-cell nucleus and presumably is affected by the presence of other nucleated cells in great numbers in intimate association with the liver strands. These nucleated cells (red or white) never show any signs of injury due to the presence of the chloroform.

Phosphorus, in its action upon the liver-cell, attacks the *cell protoplasm*, in marked contrast to chloroform. A study of the livers in such animals will be of interest in this connection, and we hope to report on this point in the near future. Some preliminary experiments give no evidence of any marked protection against phosphorus in the case of young pups, pigeons and frogs. Phosphorus is a true hepatic poison, but of a protoplasmic type. The presence of nucleated cells in association with the liver cells gives no increased resistance against this protoplasmic poison.

Method.

The animals were placed in a glass jar (capacity 7 liters) with a fairly close-fitting cover. Chloroform vapor was introduced by forcing air through chloroform into this jar until the concentration was sufficient to produce deep surgical anæsthesia. The animal was allowed to remain in this vapor, which was renewed as occasion demanded to maintain continuous surgical anæsthesia. The extent of the anæsthesia in pigeons was determined by their eye reflexes. When the eye reflexes were absent, surgical operations could be performed with no evidence of pain. The type and extent of the respiratory movements were best observed by noting the movement of the short feathers in the anal region.

The extent of anæsthesia for the frogs was determined by a loss of the motility of the legs. The respiratory movements often ceased before motility was lost. Noting the heart pulsation was most important. The terrapin was considered under chloroform anæsthesia when mechanical stimulus of its extremities aroused no movement. The chloroform used was manufactured by Mallinckrodt (M. C. W.) "for anæsthesia." The tissues of all these animals were hardened in 10 per cent formalin for 24 hours. Frozen sections were cut and stained for fat (Herxheimer's fat stain) and with hæmatoxylin and eosin. Paraffin sections were stained by various methods.

Bird III.

Feb. 20.	Chloroform anæsthesia,	30 min.	Vomited before and after anæsthesia.
Feb. 26.	Chloroform anæsthesia, 1 hr.	45 min.	Vomited and had convulsions.
Feb. 27.	Chloroform anæsthesia, 1 hr.	45 min.	Vomited and had convulsions.
Feb. 28.	Chloroform anæsthesia, 3 hrs.	35 min.	Vomited and had convulsions.
	Total anæsthesia, 7 hrs.	35 min.	

Autopsy, March 1. Gross examination: On section liver shows a yellowish tinge at the edge. The other organs are normal. Microscopical section: The liver cells are normal. There is no hyaline necrosis. There are groups of mononuclear and eosinophilic cells about the portal tissues. There is no regularity of distribution of the fat globules in the liver cells.

BIRD IV.

Feb. 20.	Chloroform anæsthesia,	20 min.	Vomited before anæsthesia.
Feb. 23.	Chloroform anæsthesia,	25 min.	Vomited before and after anæsthesia.
Feb. 26.	Chloroform anæsthesia, 3 hrs.	14 min.	Vomited before and after anæsthesia.
Feb. 27.	Chloroform anæsthesia,	10 min.	Vomited before and after anæsthesia.

Total anæsthesia, 4 hrs. 9 min.

Bird No. IV died under chloroform anæsthesia. It could not be revived by artificial respiration. Autopsied at once.

Autopsy, Feb. 27. Gross examination: All the organs appear normal. Microscopical section: The liver cells are normal. Fat stains show small evenly distributed fat droplets in the liver cells.

BIRD V.

April 1.	Chloroform anæsthesia, 2 hrs.	Convulsions and dyspnœa.
April 2.	Chloroform anæsthesia, 3 hrs.	Very quiet.
April 3.	Chloroform anæsthesia, 2 hrs.	Vomited yellowish material.

Total anæsthesia, 7 hrs.

Autopsy, April 5. Female bird; weight 295 grams. Gross examination: All the organs look normal except the liver. The liver is small and very dark red in color. Microscopical section: The liver cells and stroma are normal. The fat stains show small globules of fat of irregular size scattered sparsely throughout in the liver cells.

The following birds were bled just before anæsthesia:

BIRDS VI (a, b and c).

April 2.	Bled 3 cc.	Chloroform anæsthesia, 3 hrs.	Vomited and had convulsions.
April 4.	Bled 8 cc.	Chloroform anæsthesia, 3 hrs.	Had convulsions.
April 6.	Bled 2 cc.	Chloroform anæsthesia, 3 hrs.	Very weak and easily anæsthetized.

Total anæsthesia, 9 hrs.

Autopsies, April 8. Adult birds. Gross examination: All organs are normal but anæmic. Microscopical section: The liver cells are normal. There is no hyaline necrosis. The lobules are regular. The fat stains show small fat globules evenly scattered in the liver cells.

These three birds were kept under similar conditions and given anæsthesia together for the same periods. They were autopsied at the same time and the findings were identical. There was no obvious liver injury and not the slightest evidence of any nuclear injury.

BIRD VII.

May 14.	Chloroform anæsthesia, 3 hrs.	Bled 2 cc.	Vomited.
May 15.	Chloroform anæsthesia, 2 hrs. 30 min.	Bled 2 cc.	Quiet but weak.

Total anæsthesia, 5 hrs. 30 min.

Autopsy, May 15. Bird died under anæsthesia. Gross examination: Young, rather small bird. All the organs are normal except the liver which has a distinct yellow tinge. Microscopical section: The liver cells are normal except that they are filled with small vacuoles. The fat stain shows an increase of fat globules in the periphery of the liver lobule. The fat droplets are larger than those in normal tissue.

BIRD VIII.

May 14.	Chloroform anæsthesia, 3 hrs.	Bled 2 cc.	Very quiet.
May 15.	Chloroform anæsthesia, 3 hrs.	Bled 2 cc.	Vomited green material.
May 16.	Chloroform anæsthesia, 3 hrs.		Convulsions.

Total anæsthesia, 9 hrs.

Autopsy, May 20. Male bird, weighed 300 grams. Gross examination: All the organs are normal. Microscopical section: The liver cells are normal, and the lobules are regular. The fat stain shows small droplets of fat scattered in the liver cells. No cell necrosis.

Bird VIII does not show as much fat in the section as does Bird VII, but Bird VIII was under chloroform anæsthesia three hours longer.

BIRD I, CONTROL.

Male bird, weight 375 grams. The bird was killed with chloroform. Autopsy showed all organs normal. Microscopical sections: The liver cells and stroma are normal. The fat stains show small irregular-sized fat droplets scattered through the liver cells in all parts of the lobules.

BIRD II, CONTROL.

Female bird, weight 340 grams. Autopsy showed all organs normal except the pancreas, which was small and nodular. Microscopical sections: The liver sections show normal tissue. Fat stains show very small, evenly distributed fat droplets in the liver lobules. The pancreas shows an advanced grade of chronic cellular pancreatitis.

FROGS X (a, b and c).

Mar. 19.	Chloroform anæsthesia, 1 hr. 25 min.	Very quiet.
Mar. 20.	Chloroform anæsthesia, 2 hrs.	Very quiet.

Total anæsthesia, 3 hrs. 25 min.

Mar. 21. X-a dead

Autopsy, March 21. Large frog. Gross examination: All organs are normal in gross. Microscopical sections: The liver cells and stroma are normal. Brownish black pigment is scattered diffusely in the liver cells.

Two other frogs (X-b and c) kept under the same conditions except that they were anæsthetized one hour longer, 4 hours and 25 minutes in all. Autopsy two days later showed normal organs in gross and microscopically.

FROG XI.

May 14.	Chloroform anæsthesia, 3 hrs.	
May 15.	Chloroform anæsthesia, 3 hrs.	
May 16.	Chloroform anæsthesia, 2 hrs. 30 min.	

Total anæsthesia, 8 hrs. 30 min.

Autopsy, May 16. Female frog. Large size. Died while under anæsthesia and could not be revived. Gross examination: All organs were normal except the spleen, which was greatly swollen. The disease known as "red leg" was prevalent among the laboratory frogs, and this animal was suffering from this disease. Microscopical sections: The liver cells are normal. There is no evidence of hyaline necrosis. The fat stains show an increase in the number of fat droplets, especially in the pigmented areas. The pigment was increased in amount.

FROG XII.

May 14.	Chloroform anæsthesia, 3 hrs.	Quiet, no struggling.
May 15.	Chloroform anæsthesia, 3 hrs.	Quiet, no struggling.
May 16.	Chloroform anæsthesia, 3 hrs.	Sluggish.

Total anæsthesia, 9 hrs.

Autopsy, May 17. Large female frog. Gross examination: All organs are normal. Microscopical sections: The liver cells are normal and show no necrosis. The fat stains show the small fat globules in the pigmented areas, the normal picture.

FROG IX, CONTROL.

Autopsy, May 20. Normal frog of large size. Gross examination: All the organs are normal in gross. Microscopical sections: The liver cells are normal. Clumps of blackish brown pigment are scattered among the liver cells. The fat stain shows a few small fat globules in the clumps of black pigment.

TERRAPIN XIV.

Mar. 20.	Chloroform anæsthesia, 2 hrs. 30 min.	
Mar. 21.	Chloroform anæsthesia, 2 hrs.	

Total anæsthesia, 4 hrs. 30 min.

Autopsy. March 22. Terrapin the size of a man's hand. Gross examination: Organs are normal. Microscopical sections: The liver cells are normal. The pigment is normal in amount. The fat stains show only the normal amount of fat globules.

TERRAPIN XV.

April 29.	Chloroform anæsthesia, 7 hrs.
April 30.	Chloroform anæsthesia, 7 hrs.
May 1.	Chloroform anæsthesia, 7 hrs.
May 2.	Chloroform anæsthesia, 7 hrs.
May 3.	Chloroform anæsthesia, 7 hrs.
May 4.	Chloroform anæsthesia, 7 hrs.
May 6.	Chloroform anæsthesia, 7 hrs.
May 7.	Chloroform anæsthesia, 7 hrs.
May 8.	Chloroform anæsthesia, 7 hrs.
May 10.	Chloroform anæsthesia, death
	Total anæsthesia, 63 hrs.

Terrapin No. XV died under anæsthesia.

Autopsy, May 10. Large terrapin. Gross examination: All organs normal except the liver. The liver is of lemon yellow color with pin-point black spots. Microscopical sections: The liver cells show a great increase in the number of fat vacuoles present. There is no cell necrosis, nor nuclear degeneration. The fat stains show a marked increase in fat droplets in the liver cells.

TERRAPIN XIII.

Autopsy, April 25. Small terrapin. Gross examination: All organs are normal. Microscopical sections: The liver cells are normal. Blackish pigment is scattered through the liver cells. The black pigment is found also in large clumps. The fat stains show few fat globules in the liver cells, scattered throughout the lobules.

SUMMARY.

Chloroform anæsthesia for long periods of time produces no liver necrosis in the case of the pigeon, frog and terrapin. The liver-cells of these animals, in contrast to those of mammals, have a peculiar resistance to the poisonous action of chloroform which affects particularly the cell nucleus. Fetuses and young pups show a similar but less striking resistance on the part of the liver-cells. In both instances it is conceivable that this resistance to late chloroform poisoning is due to the presence of numbers of nucleated cells in intimate association with the liver-cell columns. These nucleated cells show no evidence of any nuclear injury. Production of a moderate grade of anemia in pigeons causes no change in the resistance to chloroform. Prolonged surgical anæsthesia (chloroform) for many hours may give rise to a certain amount of fatty degeneration (terrapin) but no demonstrable cell necrosis and nuclear degeneration.

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CLINICAL AND BACTERIOLOGICAL STUDIES ON ENDOCARDITIS LENTA.*

By RALPH H. MAJOR, M. D.,

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During the past few years the members of the medical staff in this hospital have had their attention drawn frequently to a form of endocarditis which more recent studies have tended to establish as a definite clinical entity. This type of endocarditis, which in this country has been usually known as "subacute infective endocarditis," is also designated "endocarditis lenta" by many observers, especially in Germany. The organism causing this type of endocarditis was first carefully studied by Schottmüller[1] in 1903, who gave it the name *Streptococcus viridans.* Later in 1910 he[2] proposed the name "endocarditis lenta," and laid stress upon this disease as a form of endocarditis to be sharply differentiated from the other forms either, acute or chronic, due to the ordinary *S. pyogenes.* Following Schottmüller, the work of Horder[3] and of Libman,[4] Billings[5] and Rosenow[6] in this country, has done much to clear up this subject and has greatly extended our clinical and bacteriological knowledge.

In the past year we have had, in the medical wards, five probable cases of endocarditis lenta, in three of which the presence of the *S. viridans* in the blood stream made the diagnosis certain. Interest in these cases led to an investigation of the records of the hospital in order to determine how frequent this disease has been in the past and to collect all the cases which we have had. The study of the earlier cases in the hospital has been somewhat difficult, since the attention of the observers at that time was not called particularly to this disease as an entity, and also because its bacteriology was not so well understood. In studying the histories a number of very probable cases have not been included, because the blood cultures were either negative or the organisms isolated were not described in sufficient detail to permit their identification as the *S. viridans.*

In all, there have been fifteen cases of chronic endocarditis. Of this number four gave negative blood cultures, one showed a pneumococcus, two cases were due to a streptococcus not identified definitely, and in one very interesting case reported by MacCallum and Hastings,[7] the *Micrococcus zymogenes* was isolated and described for the first time. In six cases a coccus corresponding culturally to the *S. viridans* was isolated and in this report only these six cases which are indisputable examples of this disease are included. Three of these six cases were admitted during the past year. This apparent preponderance of cases in the past year was doubtless due, in part at least, to the fact that our past experience and better knowledge of this disease at present has put us more "on the lookout," as it were, for such cases.

* From the Medical Clinic, The Johns Hopkins Hospital.

A brief résumé of the clinical course of these cases is as follows:

CASE I.—Med. No. 21969. E. D., male, age 22. Admitted to the hospital on December 17, 1907.

Complaint.—Fever, pain in joints.

Family History.—Negative.

Personal History.—General health poor. Rheumatic fever in 1892 and again in 1905. In 1907 patient was told by his physician that he had "heart trouble."

Present Illness.—Began with pains in his chest and shortness of breath, which the patient first noticed in November, 1905. In the spring of 1906 he had fever, marked dyspnea and the diagnosis of endocarditis was made. He has had fever constantly since. Complains of great weakness. In August, 1907, he had a polyarthritis.

Physical Examination.—On admission the patient showed an enlarged heart, systolic bruit at apex, diastolic murmur at base. Marked anemia. No arthritis.

Blood count: R. B. C., 5,000,000; W. B. C., 16,200; Hb., 55 per cent (Sahli).

Urine: Clear, specific gravity 1022, albumen present, no red blood cells.

Blood culture on December 20, 1907, showed *S. viridans.*

On December 21, 1907, patient had a sudden right hemiplegia with aphasia.

Patient had fever constantly, irregularly, varying from 98° F. to 104° F., usually showing evening rises. No chills. He gradually grew weaker and died, after convulsions, on February 20, 1908.

Duration of illness, two years and three months.

Anatomical Diagnosis.—Acute aortic and mitral endocarditis. Acute diffuse nephritis. Acute splenic tumor. Cardiac hypertrophy and dilatation. Bronchopneumonia. Multiple infarcts in brain, spleen and kidneys.

CASE II.—Med. No. 23699. E. S., female, aged 24. Admitted to hospital on February 10, 1909.

Complaint.—Pain in left leg, weakness.

Family History.—Negative.

Personal History.—Patient has never been very strong. Rheumatic fever and chorea in 1899. Marked polyuria the past year, averages eight voidings during the night.

Present Illness.—Patient has felt quite weak for three months. Two months ago began to have pain in knees and ankles. Has had fever constantly since December, 1908.

Physical Examination.—Very pale. Heart enlarged, systolic bruit at apex, diastolic murmur at base. Some swelling and redness of both ankles.

Blood count: R. B. C., 4,320,000; W. B. C., 8650; Hb., 67 per cent (Sahli).

Urine: Negative.

Blood culture on February 11, 1909, and again on February 17, 1909, showed *S. viridans.*

Temperature during stay in hospital was never very much elevated, was irregular, varying from 98° F. to 100° F.

Patient was discharged on February 18, 1909, and went home.

CASE III.—Med. No. 23954. C. I., female, age 37. Admitted to hospital April 8, 1909.

Complaint.—Weakness.

Family History.—Negative.

Personal History.—Pneumonia seven years ago. No history of rheumatic fever. Has suffered from "catarrh of the throat" for many years. Five years ago she had a sudden attack of shortness of breath and palpitation of the heart.

Present Illness.—Onset in November, 1908, five months before admission, with deep pains in the muscles of the trunk. Has had fever and occasional chills since. No arthritis. She has noticed increasing shortness of breath and palpitation of the heart the past month.

Physical Examination.—Pale. Heart somewhat enlarged. Presystolic and systolic murmur at apex. Fingers clubbed. Spleen palpable.

Blood Count: R. B. C., 3,000,000; W. B. C., 10,200; Hb., 55 per cent (Sahli). Later leukocyte counts varied between 7000 and 10,000.

Urine showed constant presence of albumen and casts. No red blood cells.

Blood culture on April 10, 1909, showed *S. viridans.*

Temperature during stay in hospital was very irregular, varying between 98° F. and 103° F.

Patient was discharged on April 21, 1909.

CASE IV.—Med. No. 27998. D. S., female, age 30. Admitted to hospital October 4, 1911.

Complaint.—Fever.

Family History.—Negative.

Personal History.—Patient had an attack of arthritis, probably rheumatic fever, at the age of four, in 1885. Frequent attacks of sore throat. No history of chorea.

Present Illness.—Onset three months before admission, with loss of appetite, malaise, headache, chills and irregular fever. Six weeks before admission patient's left ankle was swollen, red, hot and painful. This condition of the ankle lasted for two weeks. She has had frequent night sweats.

Physical Examination.—Pale, heart enlarged. Systolic murmur at apex. R. B. C., 3,800,000; Hb., 65 per cent (Sahli). W. B. C. on admission were 6000, varying later between 6000 and 25,500, slowly increasing during the course of the disease.

Urine showed constant presence of albumen and casts.

On October 10, 1911, there appeared a profuse crop of petechiæ over the arms and legs. October 26, 1911, patient had a sudden left hemiplegia. Following this there was a marked euphoria. Patient gradually became weaker, more and more drowsy, and died on November 20, 1911.

Temperature was irregular, fever remittent, varying between 99.5° F. and 104.2° F.

No autopsy permitted.

Total duration of illness, three months.

CASE V.—Med. No. 28504. E. G., male, age 48. Admitted to hospital on January 25, 1912.

Complaint.—Loss of weight. Swelling of legs.

Family History.—Negative.

Personal History.—Patient had a severe attack of sore throat in 1887. No history of rheumatic fever. One attack of gonorrhœa.

Present Illness.—Onset about September 15, 1911, 4 months before admission. Patient felt weak, lost his appetite and shortly afterwards noticed that the tips of his fingers were swollen and painful. A few days later he began to have marked polyuria and mycturia. He has had some fever and occasional chills since October, 1911.

Physical Examination.—Emaciation, anemia, cardiac enlargement, systolic bruit at apex, clubbing of fingers. Numerous small petechiæ in conjunctiva, over the body and extremities. Spleen not palpable.

Blood count: R. B. C., 2,900,000; W. B. C., 11,800; Hb., 52 per cent (Sahli). The leukocyte count gradually increased to 23,400 two days before death. Wassermann reaction positive.

On January 31, 1912, a pleurisy with effusion developed.

S. viridans was isolated from the blood January 27, 1912 and February 2, 1912, and from the pleural effusion on January 31, 1912.

Urine had a specific gravity varying from 1009 to 1012. Albumen and casts constantly present. Numerous red and white

blood cells. Phenolsulphonephthalein excretion—10 per cent in four hours.

The patient rapidly grew weaker, marked dyspnea developed, he became drowsy and apathetic and died February 5, 1912.

Temperature very irregular, remittent, varying from 96° F. to 104° F.

Duration of illness, four months.

Anatomical Diagnosis.—Acute ulceration and vegetative mitral endocarditis, mural thrombi in right ventricle and left auricle. Infected thrombi of posterior coronary artery, multiple thrombi in branches of right pulmonary artery. Septic and healing infarcts of spleen. Healing infarcts of kidneys, acute diffuse nephritis, acute and chronic perisplenitis, acute fibrinous pleurisy, acute splenic tumor.

Case VI.—Med. No. 82534. E. B., male, age 21. Admitted to hospital on March 27, 1912.

Complaint.—Pain about the heart, tender joints, stuttering.

Family History.—Negative.

Personal History.—Scarlet fever as a child. Frequent attacks of tonsillitis. Has had some palpitation of the heart the past two years. No history of rheumatic fever. His physician told him seven years ago that he had "heart trouble."

Present Illness.—On February 21, 1912, patient noticed a swelling of the left ankle and that the tip of his left ring finger was swollen and red. Soon afterwards a painful lump appeared above the right knee, then a round red spot on the back of the right wrist. One week later there appeared a swelling with tenderness of the right ring finger tip. Fever and chilly sensations since onset of illness. Four days before admission the patient had a sudden attack of stuttering which still persists.

Physical Examination.—Pallor, increased cardiac dullness, systolic murmur at apex. Dicrotic pulse. Clubbed fingers.

Blood count: R. B. C., 4,464,000; W. B. C., 25,500; Hb., 65 per cent (Sahli).

The leukocyte count varied between 15,000 and 28,000. Wassermann negative.

Urine: Albumen and casts constantly present, at times many red blood cells.

Blood cultures taken on March 29, 1912 and on May 1, 1912, showed *S. viridans*.

Patient gradually grew weaker, temperature irregular, varying from 98° F. to 104° F. On May 1, 1912, patient developed a sudden right hemiplegia with aphasia, which persisted until his death on May 28, 1912.

Anatomical Diagnosis.—Subacute infective endocarditis of mitral valve and wall of left auricle. Acute and chronic myocarditis. Recent and organizing infarctions of spleen and kidneys. Acute diffuse nephritis. Emaciation. Chronic adhesive pleuritis (left).

Duration of illness, 3 months.

The clinical course of all these cases shows, as do the cases reported in the literature, a remarkable similarity. Few diseases, in fact, present a more constant stereotyped picture. The onset is usually insidious, the symptoms so vague at the beginning that the patient is unable to say just when his illness began. There is often a gradually developing shortness of breath, a sense of lassitude which increases until the patient takes to his bed, accompanied by some elevation of temperature and vague pains in the joints. Painful red swelling of the finger tips, which is emphasized by Osler[9] as of great diagnostic importance, was an early sign in two cases.

The anemia, usually of a secondary type, was well marked in our cases, the hemoglobin readings varying between 50 per cent and 67 per cent (Sahli). Most of the patients have at some time during admission shown a leukocytosis varying from 10,000 to 28,000, although one case showed only 8650 and in another case the white cell count fell at times as low as 6000.

Well defined heart murmurs were constantly present in the cases of this series. All of the six cases showed involvement of the mitral valve; two of the cases had in addition an aortic lesion.*

Later in the course of the disease evidences of embolism became apparent, such as petechiæ on the skin, cerebral emboli with hemiplegia and aphasia, and emboli to the kidneys producing acute nephritis, occasionally with hæmaturia. Four of the six cases showed evidences of cerebral embolism. This complication was present in five of the eight cases reported by Lenhartz,[9] in three of the ten cases reported by Osler [l.c.] and in twenty-two of one hundred and fifty cases of endocarditis studied by Horder.[l.c.] All of the cases except one gave evidence of nephritis during life and the three cases which came to autopsy showed an acute diffuse nephritis. In two cases polyuria was one of the earliest and most constant symptoms.

Case V was of some interest in showing a pleurisy with effusion during its course. The aspirated fluid was clear and from it a pure culture of *S. viridans* was isolated.

The importance of a previous history of rheumatic fever in these cases has been emphasized by many observers. In this series, three of the six cases gave a history of an old rheumatic fever and the three cases which gave a negative history had suffered from frequent attacks of tonsillitis.

The duration of the illness in all of our cases was long, varying from three months to two years, the average duration being seven months.

All of these cases of endocarditis lenta which we have been able to follow died. This also agrees with the experience of Libman, who has found the disease invariably fatal when the presence of the organisms in the blood stream has been demonstrated. Lenhartz [l.c.] reports the recovery of one patient who, however, died later from her old *Herzleiden*. Jochmann[10] also reports two recoveries. Lorey[11] has recently reported a very interesting case with a sudden onset in which the *S. viridans* was obtained from the blood culture. This patient, after remaining in the hospital for four months, was discharged as recovered and three months later was still well. These four cases are apparently the only ones reported in which recovery took place.

The diagnosis in this disease, as has been often emphasized,

* In one probable case this year, not included in this series because of the fact that the blood cultures were constantly negative, a definite murmur was never audible. This patient ran a characteristic course for endocarditis lenta, was ill seven months and finally died several days after a cerebral embolism. An autopsy was not permitted. This patient had a rapid irregular heart, but persistent examination failed to reveal a definite heart murmur. This condition is readily explained by the tendency of the vegetations in this disease to be numerous on the walls of the heart at the base of the valves, while the lines of closure are often spared. Libman has called especial attention to this localization of the heart vegetations.

can be made positively only upon the presence of the *S. viridans* in the blood. When this organism has been isolated we can almost invariably foretell the outcome of the illness, even to prophesying the probable occurrence of cerebral embolism. It has been abundantly proved, however, that some cases of endocarditis lenta may give negative blood cultures during life, in spite of repeated attempts, although the *S. viridans* may be isolated from the heart valves after death. I have seen one such case during the past year.

In contrast to the clear-cut picture of this disease which clinical study presents to us, the bacteriological studies of the organism isolated show a very great divergence of opinion. These differences are in great measure due to the confusion which surrounds any classification of the streptococci and particularly to the difficulty with which streptococci are differentiated from pneumococci. Schottmüller, Libman, Lorey, Lenhartz and most of those who have worked with this organism, regard it as a streptococcus, while Rosenow,[l.c.] as the result of extensive studies, considers the coccus which he has isolated from cases of chronic endocarditis to be an altered pneumococcus.

During the past few years there has been much discussion as to whether there are many strains of streptococci or whether they are all to be regarded as one single race. Marmorek [12] has championed the unitarian view and believed all streptococci to belong to one group, basing his views mainly upon the fact that one strain would produce immunity in animals against other strains. More recent studies, while confirming the close relationship which exists between streptococci as a group, have, however, shown well-marked varieties and numerous attempts at classification have been made, based upon different characteristics.

Schottmüller [1] has proposed a classification based upon difference in growth on blood-agar and distinguishes three forms:

1. *S. longus seu erysipelatos,* which produces a clear zone of hemolysis about the colonies.

2. *S. mitior seu viridans,* which grows with the production of a green pigment upon the blood-agar. This organism he considers the etiological factor in endocarditis lenta.

3. *S. mucosus,* which grows with the formation of sticky mucoid whitish colonies. This organism possesses huge capsules, ferments inulin, and is regarded by most bacteriologists as a form of pneumococcus.

Andrewes and Horder,[13] as the result of extensive studies upon some twelve hundred varieties of streptococci, distinguished four types which they classify according to variations in power of fermenting carbohydrates with acid production. Their classification is as follows:

	Milk clot.	Neutral red.	Saccharose.	Lactose.	Raffinose.	Inulin.	Salicin.	Corallerrin.	Mannite.
S. pyogenes	0	0	+	+	0	0	±	0	0
S. salivarius	+	±	+	+	±	0	0	0	0
S. anginosus	+	±	+	+	0	0	0	0	0
S. fecalis	+	+	+	+	0	0	+	+	+
Pneumococcus	±	0	+	+	±	±	0	0	0

Further work upon this subject by Ainley Walker,[11] Beattie [10] and others has cast some doubt upon the value of these tests, since they have shown marked differences in the ability of the same streptococcus to ferment certain sugars when cultivated over long periods of time. Winslow [9] believes these tests to be of considerable importance in differentiating between intestinal streptococci of man, the horse and the cow, and Ainley Walker states that "it is not denied that the reactions may often yield very useful evidence as to the natural or recent habitat" of streptococci.

We have studied our cultures along both lines and have also endeavored to find, if possible, whether these organisms are modified pneumococci, such as those described by Rosenow. For this work the three cultures obtained from patients Nos. IV, V and VI have been used, one culture obtained outside and a fifth culture kindly sent by Dr. Ladd of Cleveland, who isolated it from the blood of a patient with endocarditis. All of these organisms have shown a great similarity in their cultural reactions.

The organisms, when first isolated in blood cultures, grew very feebly, appearing on the blood-agar only after 48 hours, and in one case only after six days. On the blood-agar plates they grew with the production of a definite greenish pigment, when viewed by direct light and surrounded by a very slight clear zone of hemolysis in marked contrast to the wide zone of hemolysis produced by the *S. pyogenes.* This production of green has also been constant in subcultures when the organisms are grown at varying levels throughout a blood-agar plate, while if simply inoculated upon the surface, the colonies are frequently whitish and show no tendency to form the greenish pigment. The intensity of the green also seems dependent in part upon the amount of blood in the medium.

The organism grows as a very small coccus which is Gram positive, shows no capsules and produces, as a rule, long chains varying from ten to twenty cocci in length on an average. In broth the coccus grows with the production of a granular deposit at the bottom of the flask, although after being grown upon artificial medium, it often produces a diffuse turbidity. In glucose broth it grows very luxuriantly. In litmus milk, acid and clotting were produced in 24 to 48 hours by all the cultures except one, which was isolated from patient No. IV, and has never produced any change, although it grows quite well in this medium. Upon serum glucose agar all of the cultures produced a marked white precipitate around the colonies. No gas was formed in glucose agar.

We have never had sufficient evidence to consider these organisms as altered pneumococci. Capsules have never been demonstrated in any of the cultures as obtained from the patient, after prolonged cultivation for ten months, in the peritoneal fluid or heart blood of animals dead from experimental infection, or in subcultures which had passed through animals.* Similarly, none of these procedures has changed its morphology or lessened its ability of form chains. One strain

* In staining for capsules we have used Welch's method and Rosenow's l. c. method. Capsulated pneumococci when incubated with normal serum for two hours show excellent capsules, easily demonstrated by Wilson's stain or gentian violet. Our cultures

which has been grown upon artificial media for ten months and passed through mice, has constantly produced, and still forms, long chains of forty or more cocci when grown in glucose broth. None of the cocci has fermented inulin when first isolated or upon subsequent subcultures and passage through mice.

Upon the serum glucose agar medium, recommended by Libman as a valuable method of distinguishing streptococci from pneumococci, the organisms, as already stated, grew with the production of a deep white precipitate in the medium. Five strains of typical pneumococci showed only a very slight, almost imperceptible clouding. These organisms have also been tested for their solubility in bile, according to the method of Neufelt," and do not dissolve, while typical virulent pneumococci do.

The study of these cultures along the above lines leads us to regard them as streptococci, belonging to the *S. viridans* group of Schottmüller, and they are probably identical with the organism described by Libman as the "endocarditis coccus."

These streptococci, examined with reference to the classification of Andrewes and Horder, showed the following reactions upon the various media.

	Milk clot.	Saccharose.	Lactose.	Raffinose.	Inulin.	Salicin.	Mannite.
1	0	+	0	+	0	+	0
2	+	+	+	+	0	+	0
3	+	+	+	+	0	0	0
4	+	+	+	+	0	0	0
5	+	+	+	+	0	0	0

These tests have been repeated frequently over a period of four months and have shown no change in fermentation reactions. For these tests 1 per cent of the various substances in sugar free broth or hydrocele broth was used. The chemicals were obtained from Merck & Co. and acid fuchsin was used as an indicator. Subcultures were subsequently made in each instance from the tubes and examined, to guard against defective growth or contamination.

Except for salicin, the fermentation reactions were the same for all the organisms, with the notable exception of No. 1, which did not ferment lactose. This also, it may be remarked, is the same culture which produces no acidity or coagulation in milk, depending possibly upon this inability to attack lactose.

In classifying these cultures according to the plan of Andrewes and Horder, it is apparent that our organism is not the *S. anginosus,* which is a hemolyser. The fact that it does not produce hemolysis, forms a clot in milk and ferments raffinose, excludes it as a *S. pyogenes.* This forces it into either the *S. salivarius* or the *S. fecalis* group and it does not belong to the latter group since this is distinguished by the "arbitrary mannite test"—the ability to ferment mannite. This leaves only the *S. salivarius* group as the possible class to which it may belong. "Short chains in broth which is rendered uniformly turbid," which Andrewes and Horder state is characteristic of the *S. salivarius,* is not an apt description of the growth of our culture in broth, and none of the variants described by them corresponds to our culture No. 1.

Andrewes and Horder also state that the "distinction between it (*S. salivarius*) and *S. anginosus* rests only upon the somewhat shadowy character of length of chains and lesser virulence," which is certainly of much less importance than the fact that the *S. anginosus* like "*S. pyogenes* is markedly hemolytic."

However, without laying too much stress upon differences in fermentation powers, the organism which we are studying does belong to the non-hemolysing group of streptococci, and if we accept the fermentation of mannite as an arbitrary distinction then it belongs to the *S. salivarius* group of Andrewes and Horden.

The frequency with which these cases of endocarditis lenta give an old history of rheumatic fever and the tendency which some cases of rheumatic fever show to develop into "malignant endocarditis," suggests at once a possible relationship between the infecting agents of the two diseases and also, more strongly, the doubt whether some cases diagnosed as rheumatic fever may not really represent the initial stage of endocarditis lenta. Some of the cases of rheumatic fever which die and at autopsy show streptococci in the cardiac vegetations would present some difficulties in a differential diagnosis from endocarditis lenta. It seems very probable that the veins of acute rheumatic fever is as yet undiscovered; the cocci thus far described may very well be secondary invaders.

We have never succeeded in isolating the *Micrococcus rheumaticus* from the blood stream of any patient in this hospital suffering from rheumatic fever, although blood cultures have been made upon such cases as a routine the past few years. However, as is well known, Poynton and Paine" have described a coccus, the *M. rheumaticus,* obtained from the blood and joints of rheumatic patients, which they consider the specific organism. Through the kindness of Dr. Winslow (curator of the American Museum of Natural History, N. Y.) we have received three cultures supposed to be the *M. rheumaticus.* No. 254 was obtained originally from Dr. J. M. Beattie, No. 34 from Dr. Paine and No. 399 from Dr. Lentz. These organisms we have studied along the same lines as the streptococci already considered.

These organisms produce green upon blood-agar, and the colonies are surrounded by a very slight clear zone. The coccus is very minute, grows in long chains, is Gram positive, shows no marked hemolysis as does the *S. pyogenes,* coagulates milk and produces a dense white precipitate on serum glucose agar. It does not ferment inulin and is not dissolved by bile. These cultural reactions are all common to the *S. viridans* and from them no distinguishing point is seen

stained by this method have also failed to show capsules. This "incubation method" devised by Dr. Leutscher and Dr. Clough, has been used the past year in the laboratories of the Biological Division of the Medical Clinic here, with excellent results.

between the two organisms. Rosenow[l.c.] has also remarked that they show similarities.

These strains, tested by the fermentation reaction, showed the following results:

	Glucose.	Saccharose.	Lactose.	Raffinose.	Inulin.	Salicin.	Mannite.
254	+	+	+	0	0	+	+
34	+	0	+	0	0	0	0
399	+	+	+	0	0	+	+

Following the classification of Andrewes and Horder, Nos. 259 and 399 are examples of the *S. fecalis,* while No. 34 belongs to the *S. salivarius* group. This agrees with the results of these two workers, who found that the examples of the "rheumococcus" studied by them, belonged to either the *S. salivarius* or *S. fecalis* group.

The *S. viridans* is easily distinguished from the *M. zymogenes* of MacCallum and Hastings,[l.c.] which, as previously stated, was obtained from a case of chronic endocarditis in this hospital. The *M. zymogenes,* according to their description and the later studies of Harris and Longcope,[19] liquefies gelatin, produces marked peptonization of the clot formed in litmus milk and also peptonizes blood serum. We have studied a culture of the *M. zymogenes* and can confirm these striking properties of this organism, which the *S. viridans* does not possess.

The principle of complement fixation discovered by Bordet and Gengou, which has been used with such signal success in the diagnosis of syphilis and which has been employed so extensively for testing the presence of antibodies in various diseases, has not as yet been much applied in endocarditis lenta. We had an opportunity of trying this method in Case VI.

As an antigen we used cultures of *S. viridans* obtained from the patient's blood. The cocci were grown in glucose broth for 48 hours, centrifugalized, washed, emulsified in normal salt solution, heated at 60° C. for half an hour and then allowed to remain in the thermostat at 37° C. for 48 hours. Various dilutions were then made until a dilution of 1:3 was obtained, which was not anti-complementary. This antigen, in various dilutions from 1:3 to 1:15, was able, in the presence of inactivated serum from the patient, to fix complement completely. The serum from six other patients suffering from various diseases, used as controls, showed no fixation at all. Four of these sera showed practically no normal anti-sheep amboceptor, one of them gave a positive Wassermann reaction. These experiments were repeated three times with the same clear-cut result on each occasion.

Similarly, it was found that an antigen prepared from the ordinary *S. pyogenes,* when added to the patient's serum, would also fix complement, while an antigen prepared by the same method from a pneumococcus showed no complement fixation. There was, however, no proof that this pneumococcus antigen was a "workable antigen."

Further work along these lines may show the complement fixation test of value in diagnosing cases of endocarditis lenta with persistent negative blood cultures. Also by applying this test to animals immunized against *S. viridans, S. pyogenes* and the pneumococcus, the relationship between the three organisms may be determined more accurately. Swift,[20] working with the complement fixation method in rabbits immunized with streptococci and pneumococci, found no interreaction between the two, although there was definite interreactions between different strains of streptococci. Some of the streptococci he used correspond culturally to the *S. viridans,* and this work indicates that their relationship is closer to the streptococci than to pneumococci.

CONCLUSIONS.

The results of these studies lead to the following conclusions:

1. Endocarditis lenta, caused by the *S. viridans,* has a sufficiently distinctive picture to deserve recognition as a separate clinical entity. That cases of chronic endocarditis may also be due to the *B. influenzæ, S. pyogenes,* or pneumococcus, is, of course, well known, but such cases should be distinguished from those due to the *S. viridans,* just as epidemic cerebro-spinal meningitis, for example, is distinguished from meningitis due to the *B. tuberculosis, B. influenzæ* or *S. pyogenes.*

2. The coccus present in our cases corresponds culturally to the organism described by Schottmüller as the *S. viridans.* The most valuable method at present of differentiating this coccus from the *S. pyogenes,* is by observing the green growth on blood-agar.

This organism, following Andrewes and Horder's classification, would be considered as a *S. salivarius.* This type of non-hemolysing streptococcus, is, however, distinguished from the *S. fecalis* only by the arbitrary mannite test, one of the reactions which Ainley Walker found very inconstant in the same streptococcus when tested at long intervals. If, however, further work should prove this to be a constant difference, then it may be of some value to separate the *S. viridans* into two types.

The differences which organism No. 1 shows in not changing litmus milk or fermenting lactose, are not essential but indicate simply a "variant" of the *S. viridans* group.

3. No essential cultural differences have been noted between the *S. viridans* and the *M. rheumaticus.*

4. Complement fixation tests in one case of endocarditis lenta showed the presence in the patient's blood of specific "antibodies."

In conclusion, it is a great pleasure to thank Prof. Barker and Dr. Clough for their kind assistance and advice in preparing this report.

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THE EFFECT OF SCARLET RED ON DEFECTS IN THE MUCOUS MEMBRANE OF THE STOMACH.

AN EXPERIMENTAL STUDY.

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INTRODUCTION.

While using scarlet red * in the treatment of ulcers, of varying etiology, on the skin and on mucous membranes (in cavities where local applications could be made), it occurred to us that possibly ulcers of the alimentary tract, especially ulcers of the stomach, might be benefited by the use of scarlet red, if it could be brought into contact with the ulcerated surface.

There was no reason to believe that this dyestuff would not have a definite stimulating effect on the epithelial edges of these ulcers, as local applications of this substance to sluggish ulcers of comparable size on mucous membranes in other situations caused definite epithelial stimulation and rapid healing.

All that is necessary for the healing of such an ulcer is for healthy mucous membrane to grow across its floor and remain intact, and it seemed possible that the mucous membrane of the ulcer edges might be stimulated by the scarlet red and thus accomplish the desired result.

Proceeding on these premises it seemed wise to undertake some experimental work on animals before attempting to administer this substance to a patient suffering with gastric ulcer. With this end in view the following investigations were carried out.

Part I. Preliminary Experiments.

It was important primarily to investigate the toxicity of the substance when given internally, and also to familiarize ourselves with its effect on the general health of the animals in regard to weight, excretions, hemoglobin, etc., and for this purpose a preliminary series of experiments was carried out on dogs, and on a few rabbits.

Some of the experiments will be reported in detail, in order

* *Chemistry.*—The dyestuff used in this series was manufactured by Kalle & Company, who were good enough to furnish us with a plentiful supply for experimental purposes.

Scientific Name.—Toluneazotolueneazo Beta naphthol.

Commercial Names.—Biebrich Scarlet R. Medicinal (Kalle & Co.); Oil Scarlet; Red B. Oil Soluble Extra-concentrated; Ponceau 3 B. ("Organic Colouring Matters," Schultz & Julius (Green), 1904, p. 108, No. 150.)

Method of Preparation.—It is made by a combination of amidoazotoluol and Beta naphthol, and has the formula,

$$C_6H_3(CH_3) - N = N - C_6H_3(CH_3) - N = N - C_{10}H_6OH \text{ (Beta)}.$$

Color.—It is a reddish brown powder, which gives a scarlet red color in oil solution. It cakes at about 175° C. and melts at 184° to 186° C., forming a dark bronze shiny mass. At about 260° C. decomposition takes place and heavy brown fumes are emitted.

Taste.—The powder and also the oil solution are tasteless.

Reaction.—A one per cent solution in neutral oil is neutral to litmus.

Solubilities.—It is insoluble in water and urine, even after boiling. It is soluble in alcohol, ether and chloroform, olive oil, fats, fatty oils, turpentine, warmed vaseline and paraffin.

One gram of finely divided powder heated gradually in 100 cubic centimeters of olive oil to 200° C. remained in solution for two days or more at ordinary room temperature. Approximately a two per cent solution can be made, but the scarlet red does not stay in solution for any length of time, and tends to precipitate at once on cooling.

A reaction which will specifically identify this dyestuff has not yet been discovered. There are, however, a number of color reactions with various acids, which we will not consider at this time.

The gastric juice, experimentally, has no effect on the scarlet red.

X-ray Findings.—This material casts no shadow on an X-ray plate.

Bactericidal Properties.—A luxuriant growth of *Bacillus coli* and also of *Staphylococcus aureus* was obtained in 24 hours from both agar and bouillon cultures intimately mixed with one per cent oil solution of scarlet red. This seems to show that this substance has little, if any, bactericidal property.

to give an idea of the experimental procedure and also to compare the different methods of administration.

Autopsy.—The conjunctivæ and mucous membranes were not stained. *The fat of the entire body was colored a rose pink.*

On opening the stomach (18 hours after the last administration), fine red oily globules were seen everywhere over the mucous membrane. Scarlet red was also present in the small intestine and ascending colon. Otherwise these appeared normal.

The thoracic duct contained a colorless fluid. The mesenteric and other lymphatic glands were not stained. The kidneys and bladder appeared normal. The gall bladder was normal, but the bile was a dark reddish amber color. The foam, after shaking, had a pinkish tinge. Ether and chloroform extracts gave a definite rose pink color. Microscopic examination of all tissues showed no organic change due to the dyestuff.

Dog. A.—*Fed with one per cent oil solution.* (Each cubic centimeter of oil contained 10 milligrams of scarlet red.) The animal was confined in a cage for the first three weeks and was then transferred to the yard.

Date.	Amount.	Remarks.
April 20, 1911.	5 cc.	Weight, 13¼ pounds. Mixed diet.
April 21, 1911.	5 cc.	Stool colored red.
April 25, 1911.	5 cc.	
April 26, 1911.	5 cc.	Urine examination, amber color, negative for blood, casts and albumin.
April 29, 1911.	.2 grams	
May 1, 1911.	5 cc.	Animal developed distemper.
May 3, 1911.	5 cc.	Profuse nasal discharge and deep cough.
May 4, 1911.	.....	Rather severe diarrhea.
May 5, 1911.	55 cc.	No vomiting.
May 6, 1911.	.....	Diarrhea continuous. Occult blood in stools. (Guiac test.) Microscopic examination negative, for red blood corpuscles.
May 8, 1911.	5 cc.	Condition improved.
May 11, 1911.	50 cc.	
May 12, 1911.	.....	Diarrhea still severe.
May 13, 1911.	5 cc.	Dog transferred to yard.
May 15, 1911.	5 cc.	
May 17 1911.	5 cc.	
May 20, 1911.	5 cc.	
May 22, 1911.	5 cc.	General condition improving.
May 23, 1911.	.....	Hard stool.
May 24, 1911.	5 cc.	
May 26, 1911.	5 cc.	
May 29, 1911.	5 cc.	Stool well formed.
May 31, 1911.	10 cc.	
June 1, 1911.	5 cc.	
June 3, 1911.	10 cc.	
June 5, 1911.	5 cc.	
June 7, 1911.	5 grams scarlet red in oil emulsion.	Animal vomited almost all of the emulsion.
June 9, 1911.	5 cc.	
June 13, 1911.	10 cc.	
June 16 1911.	10 cc.	
June 17, 1911.	20 cc.	
June 20, 1911.	10 cc.	
June 22, 1911.	15 cc.	Hard stools. Hemoglobin, 92 per cent. (Sahli.)
June 23, 1911.	15 cc.	
June 24, 1911.	10 cc.	
June 27, 1911.	20 cc.	Stools oily and colored red throughout the treatment.
June 28, 1911.	.....	9.30 a. m. Animal sacrificed. Weight, 13½ pounds. (Gain of ¼ pound.) General condition excellent. During the treatment the animal was given a little over 3.5 grams of scarlet red, exclusive of that vomited.
Total	325 cc.	

Comment.—This animal was given doses of one per cent scarlet red in olive oil for nearly ten weeks. The doses varied between 5 cubic centimeters and 55 cubic centimeters. The amount of scarlet red given was 3.5 grams. There was a gain of ¼ pound in spite of the fact that the animal developed a severe attack of distemper five days after the feeding began. Diarrhea commenced shortly after this and was undoubtedly due to the distemper, as it lasted during the attack and then on recovery promptly ceased, although the doses of the oil averaged larger during the latter part of the experiment.

The urine was not colored red and on several occasions examination was negative for blood, casts and albumin. The stools became red about 24 hours after the first dose of oil solution. Occult blood was found in the stools (Guiac test), but no red blood cells microscopically. This can be accounted for by the mixed diet.

In addition to the one per cent oil solution .2 grams of the powder were given in a capsule, and at another time an emulsion of 5 grams of the powder in oil, but this emulsion was vomited. There was no other vomiting noted.

Following the oil feeding the fat over the entire body was stained a rose pink. The coloring matter could also be demonstrated in the bile.

Dog B.—*Fed with dry powder.* The animal was confined in a cage throughout the treatment.

Date.	Amount.	Remarks.
April 25, 1911.	.6 gm. in capsules.	Mixed diet. Weight, 18 pounds.
April 26, 1911.	.....	Portion of stool colored a very light pink in the morning. Another in the evening, 24 hours after feeding, definitely red. Occult blood (Guiac test) otherwise negative.
April 27, 1911.	1.5 gm.	Urine examination negative.
April 29, 1911.	1.2 gm.	
May 1, 1911.	.8 gm.	Animal has nasal discharge.
May 3, 1911.	10 cc. oil solution.	Animal developed distemper. Deep cough, nasal discharge.
May 4, 1911.	.6 gm.	Slight diarrhea.
May 5, 1911.	.2 gm.	
May 6, 1911.	.8 gm.	Diarrhea continues.
May 8, 1911.	.4 gm.	
May 9, 1911.	.4 gm.	
May 10, 1911.	.4 gm.	
May 11, 1911.	.4 gm.	
May 12, 1911.	.4 gm.	Diarrhea continues.
May 15, 1911.	.4 gm.	
May 16, 1911.	.4 gm.	
May 17, 1911.	.2 gm	
May 20, 1911.	.2 gm.	
May 22, 1911.	.2 gm.	
May 24, 1911.	.2 gm.	Diarrhea less marked.
May 25, 1911.	.2 gm.	
May 26, 1911.	.2 gm.	
May 27, 1911.	.2 gm.	
May 29, 1911.	.2 gm.	Condition of animal has improved. Rather firm stool.
May 31, 1911.	.4 gm.	
June 1, 1911.	.2 gm.	
June 2, 1911.	.4 gm.	Distemper is worse. Severe deep cough and diarrhea.
June 3, 1911.	.4 gm	
June 5, 1911.	.2 gm.	Milk diet, fat meat and 10 cc. olive oil.
June 7, 1911.	.5 gm.	No vomiting. Same diet continued.
June 8, 1911.	.....	Same diet continued. Animal showed no ill effects.
June 9, 1911.	.....	Same diet continued. Animal showed no ill effects.
June 13, 1911.	.4 gm.	Moderate diarrhea continues.
June 14, 1911.	.2 gm.	
June 16, 1911.	.2 gm.	
June 20, 1911.	.2 gm.	
June 22, 1911.	5.0 gm.	Hemoglobin, 77 per cent. (Sahli.)
June 23, 1911.	.....	Distemper and diarrhea continues.
June 24, 1911.	.....	Animal has the mange. Weight, 17 lbs. (One pound loss.) Which can be easily explained by distemper and mange and confinement.
June 27, 1911.	1 gm.	
June 28, 1911.	.....	Purulent discharge from nose, and mangy over the greater portion of body, with loss of hair and erosions of skin. Animal sacrificed.
Total	19.2 gm.	

Autopsy.—Conjunctivæ and mucous membranes were clear. All the tissues appeared normal. There was no apparent staining of the body fat. The thoracic duct contained a colorless fluid. The stomach, esophagus and intestines appeared normal. The contents of the large bowel appeared rather red. The bladder and gall bladder were normal. Ether and chloroform extracts of the dark amber colored bile were colorless. The foam had a yellow tinge. Microscopic examination of all the tissues showed no organic change due to the dyestuff.

Comment.—This animal was given 19.5 grams of scarlet red powder in capsules over a period of 9 weeks. The doses

varied between .2 gram and 5 grams. There was loss of weight (one pound) which was probably due to the fact that the animal developed distemper a few days after the feeding was begun, and this continued until the termination of the experiment. There was the usual accompanying diarrhea. In addition to the distemper the animal was afflicted with mange. The examination of the urine from time to time was negative. There was no vomiting throughout the treatment. The stools became red about 24 hours after the first dose was given.

In comparing this animal with the one fed with scarlet red in olive oil, it is interesting to note that although nearly six times as much scarlet red was administered—in the dry form, there was no appreciable coloring of the body fat, and no pink color could be demonstrated in the bile. Giving a fat diet in connection with a large dose of dry powder seemed to have no effect on causing the coloring of the body fat.

Dog L. Weight 13¾ pounds. Feeding began December 19, 1911. Forty-five capsules of scarlet red, each containing .4 gram, were given between that date and January 4, 1912. Two to four capsules were given each day, 19 grams in all being given. There was no vomiting or diarrhea. No change in the color of the urine. Excellent condition until January 7, when the animal became ill.

January 9, 1912. Death from pneumonia. Weight, 10½ pounds. The loss was accounted for by illness. *Autopsy.*—The subcutaneous fat was not stained. The omental fat was stained a very faint pink color and the fat around the heart was a definite pink. The other organs showed no change worthy of note. Ether extract of the bile was colorless.

Comment.—This animal was fed 19 grams of scarlet red powder in 16 days. There was no toxic effect of any kind noted, although a large amount of the dyestuff was given in a short time. There was very slight pink staining of the omental fat and definite staining of the fat around the heart, otherwise the body fat was not stained.

In addition to the above the following large single doses were tried on other dogs.

Diet.	Amount, single dose.	Vomiting.	Other toxic effects.
Mixed.....	50 cc. oil solution.	Negative.	Negative.
Mixed.....	80 cc. oil solution.	4 cc. 2 hours after administration.	Negative.
Mixed.....	100 cc. oil solution.	5 cc. 2 hours after administration.	Negative.
Mixed.....	.5 gm. powder.	Negative.	Negative.
Mixed.....	1. gm. powder.	Negative.	Negative.
Mixed.....	1.5 gm. in oil emulsion.	Negative.	Negative.
Mixed.....	2.5 gm. in oil emulsion.	Negative.	Negative.
Milk, fat meat, olive oil.	5. gm. powder.	Negative.	Negative.

Rabbit 1.—Weight, 2¾ pounds. The rabbit was fed 1.5 grams of scarlet red (dry powder) divided and put into 18 capsules. One capsule was given each day from August 14 to September 5, 1911.

The animal was given a diet of vegetables and bread and butter. There was no ill effect noted throughout the experiment, and no diarrhea. There was no loss of weight at the end of the treatment.

September 6, 1911. Animal sacrificed. *Autopsy.*—The conjunctivæ and mucous membranes were not stained. The body fat everywhere was found to be stained a remarkable brilliant pink. The bile was of a light green color. The fat of the omentum and mesenteric attachments to the stomach and small and large intestines was likewise stained a brilliant pink. The glands were slightly enlarged, but showed no stain. The kidneys, liver and rest of the viscera showed no change worthy of note.

Rabbit 2.—The animal was fed each day with 5 cubic centimeters of one per cent scarlet red oil solution from August 19 to 25, 1911, and from August 25 to 30, 1911, with 10 cubic centimeters of one per cent scarlet red oil solution. Examination of the fat one month later showed marked pink color. Animal in good condition. *No autopsy.*

Rabbit 3.—Weight, 2¾ pounds. The rabbit was fed 5.8 grams of scarlet red (dry powder) divided and put into 24 capsules, given between December 19, 1911, and January 4, 1912. The animal was in excellent condition throughout the experiment.

January 9, 1912. Weight, 4 pounds. The subcutaneous and omental fat was examined and both were found stained a deep reddish pink.

February 14. The fat was again examined. It still remained a brilliant pink with very little, if any, diminution in intensity when compared with the specimen removed on January 9.

April 9. The omental fat was again examined. The pink color was considerably less marked than at the last examination. This seems to show that the color is gradually eliminated.

July 1, 1912. Weight, 4 pounds. Animal sacrificed. *Autopsy.*—The subcutaneous and omental fat showed no pink color. This shows that the color is gradually eliminated.

Comment.—The entire body fat in rabbits was stained a brilliant pink when fed with either the oil solution of scarlet red or the dry powder. The staining was as brilliant in the animal fed with 1.5 grams as in that fed 5.8 grams. No toxic effects whatever were noted, and the animals gained in weight during the experiments. In the course of several months there was a definite clearing up of the stained fat although this decolorization was very slow.

The Effect of Scarlet Red on Intestinal and Renal Secretions.

Dog C.—Weight, 28 pounds. Before the scarlet red feeding was begun the animal was placed on a controlled meat diet for three weeks and had consistently hard stools.

May 11, 1911. *10.30 a. m.* The animal was given 100 cubic centimeters (1 gram) of one per cent oil solution by mouth. *4 p. m.* Catheterized specimen of urine, amber color, acid. No color reaction on addition of alkali and acid. No albumin, or sugar. Microscopic examination showed no casts, or red blood corpuscles, but a few epithelial cells.

May 12. *10 a. m.* Catheterized specimen of urine. Dark brownish yellow color, acid. Same note as above. Microscopic examination showed no casts or red blood corpuscles, but a few epithelial cells and white blood corpuscles. *4 p. m.* Well formed, soft red stool. No diarrhea. No mucus, blood or straining at any time after administration. Occult blood test (Guiac) positive. This can be explained by the meat diet. Microscopic examination showed no red blood corpuscles. The subsequent stools were hard and were colored red until May 15.

Dog R.—Weight, 16 pounds. Before the scarlet red feeding was begun the animal was placed on a controlled meat diet for three weeks and had consistently hard stools.

May 16, 1911. *10 a. m.* Animal given 60 cubic centimeters (.6 gram) of one per cent oil solution, by mouth. *11 a. m.* Condition good. *1 p. m.* Condition good.

May 17. *10 a. m.* Animal in good condition. Mixed 24 hours specimen of urine was negative for usual urine tests. The stool was red and oily, well formed and firm. There was no diarrhea, mucus, blood or straining. Occult blood test (Guiac) was positive. This can be explained by the meat diet. Microscopic examination showed no red blood corpuscles. The last red stool came away the morning of May 18.

Further results showing the absence of effect on the kidneys are noted below:

Amount of S. R.	Specimen.	Time.	Reaction.	Albumin.	Blood, mic. and color.	Casts.	Oxidation.	Remarks.
100 cc. 1% oil solution.	Cath.	24 hrs.	Acid.	Neg.	Neg.	Neg.	Neg.	No color reaction on addition of alkali or acid. Ether extracts colorless.
100 cc. 1% oil solution.	Cath.	Every 4 hrs. for 24 hrs.	Acid.	Trace.	Neg.	Neg.	Neg.	Do
2.5 gm. S. R. in oil emulsion.	Mixed.	24 hrs.	Acid.	Neg.	Neg.	Neg.	Neg.	Do
20 cc. oil subcutaneously.	Mixed.	24 hrs.	Acid	Neg.	Neg.	Neg.	Neg	Do
30 cc. oil intraperitoneally.	Mixed.	24 hrs.	Acid.	Trace.	Neg.	Neg.	Neg.	Do

Comment.—Scarlet red seems to have no purgative effect whatever and causes no appreciable change in the action of the kidneys.

Remarks.—The foregoing experiments lead us to believe that the internal administration of scarlet red, either in oil solution or as dry powder, has no toxic effect, either on the economy as a whole, or on any special organ. There was no purgative action, and the urine was unchanged. There was no abnormal stimulation of the mucosa anywhere in the alimentary tract. The mucous membranes of the bladder and gall bladder were unaffected. Microscopic examination of the various organs and tissues showed no change which could in any way be traced to the dyestuff.

In order to determine the toxic effect of scarlet red in the lax subcutaneous tissue and in the peritoneal cavity the following experiments were made.

THE EFFECT OF SUBCUTANEOUS INJECTIONS.

Dog K. May 17, 1911. Animal given, subcutaneously through a needle, 20 cubic centimeters of sterilized one per cent oil solution.

May 18. Site of injection slightly swollen. No signs of inflammation. Urine and feces negative. Condition good. No signs of toxicity.

May 19. Condition good. The swelling at site of injection has disappeared.

May 22. What appeared to be a proliferation of the epithelium in the form of a papillary projection was seen at the site of the injection.

June 1. Animal sacrificed. *Autopsy.*—The loose subcutaneous tissue over a large area (size of hand), was found to be stained a bright red color. Free red oil seemed to lie between the tissue layers and came off readily on the hands and knife. The skin over this area was not affected. The muscles beneath were unchanged. No inflammatory exudate was anywhere found. No ulceration at site of the injection. Microscopic examination showed no inflammation.

Dog S.—Weight, 11½ pounds. February 27, 1912. *Operation.*—A small incision was made on each side of the mid-line of the back, and into each was injected 10 cubic centimeters (.3 gram), of a sterilized oil emulsion of scarlet red. The wounds were closed in two layers. There was no toxic effect following the operation, and no signs of inflammation.

March 28. Animal sacrificed. *Autopsy.*—In the subcutaneous tissue on each side of the back was an area about the size of the palm of the hand which was stained a brilliant red. There were pockets of free red oil between the tissue layers, and the staining of the fat was only local and by contact. The skin above and the muscles beneath were unaffected. There was no other staining noted and the examination was otherwise unimportant.

Comment.—Subcutaneous injections caused no irritation. The oil solution remained in the tissue unchanged and there was little if any absorption. There was local staining of the fat which came in contact with the oil. There were no toxic symptoms manifested.

THE EFFECT OF INTRAPERITONEAL INJECTIONS.

Dog O. May 22, 1911. Animal given, intraperitoneally through a needle, 30 cubic centimeters of sterilized one per cent oil solution.

May 23. Condition good. The urine was negative.

May 24. Animal showed nothing abnormal except thickening of the epithelium at the site of injection.

May 25. Animal appeared ill.

May 26. Condition serious. Purulent discharge from right eye. Apathetic. Walked fairly well.

May 27. Death of animal. *Autopsy.*—On opening the peritoneum the viscera were seen to be stained a bright red color. About 15 cubic centimeters of red oily fluid were readily removed from the flanks. A fibrinous exudate was found covering the omentum and portions of the visceral peritoneum. The peritoneum was plastered down to the dome of the liver by a small amount of fibrinous exudate. The peritoneum was everywhere covered with oily red fluid. No ulceration was found at the site of the peritoneal injection. All the viscera were congested, but were otherwise negative. There was no staining of fat except in the peritoneal cavity, and death was due to an acute peritonitis.

Dog C. Weight, 28 pounds. June 3, 1911. The animal was given, intraperitoneally through a needle, 10 cubic centimeters of sterilized one per cent scarlet red oil solution.

June 4-27. There were no untoward symptoms.

This animal was given in another experiment 100 cubic centimeters of oil solution, by mouth, on May 11, and 1.5 grams of scarlet red powder in oil emulsion on June 22.

June 27. Weight, 28 pounds.

June 29. Animal sacrificed. Two hours before death the animal was given 1 gram of scarlet red powder, in a capsule. *Autopsy.*—The fat over the entire body was stained a rose pink, due to scarlet red oil feedings. The mucous membranes and conjunctivæ were clear. On opening the peritoneal cavity 5 cubic centimeters of a clear yellowish fluid was found, but no free scarlet red could be seen. In the region of the spleen, and closely adherent to it, there was a mass of omentum, which on section contained numerous little pockets of oily red fluid. Altogether there was a considerable amount of the oil in these pockets, and this seemed to show that the scarlet red had been encysted like a foreign body, and that very little, if any, had been absorbed. There were several similar smaller areas scattered over the abdominal cavity. The bladder and gall bladder were normal. Ether extract of the bile was colorless. The thoracic duct contained a clear colorless fluid. The mucous membranes of the esophagus, stomach and intestines were normal. The mesenteric and other glands were not colored. The stomach contained food which was colored a rose red, and after removal of this mass the entire membrane was found to be smeared with an oily red material.

Dog M. June 20, 1911. Animal given, intraperitoneally through an abdominal incision, 10 cubic centimeters of sterilized one per cent oil solution. Death of animal in 32 hours.

Autopsy.—Showed death to be due to bilateral broncho-pneumonia. The peritoneal surface was covered everywhere with an oily fluid. No inflammatory exudate was found. The mesenteric glands showed no discoloration. There was no staining of the fat, except locally in the peritoneal cavity.

Dog N. February 27, 1912. Animal given, intraperitoneally through an abdominal incision, .8 gram of a sterilized emulsion of scarlet red in 30 cubic centimeters of olive oil.

March 19. For the first two days after the injection the animal was apathetic, and then apparently recovered perfectly and remained in excellent condition until March 18, when there was a sudden collapse. Death followed within a few hours. *Autopsy.*—The wound had healed perfectly. There was a small amount of free straw colored fluid in the peritoneal cavity. The contents of the abdominal cavity were in one compact mass, being bound together with dense adhesions, which were separated with difficulty. The entire mass was stained a brilliant red color. On separating the adhesions the scarlet red oil was found here and there in pockets, and was apparently unchanged. There were large pockets behind the liver and spleen containing 6-8 cubic centimeters of the red oil. In some places encysted masses of scarlet red were found. The body fat outside of the abdominal cavity was unstained. Except for the abdominal condition the examination was unimportant. Death was caused by general plastic peritonitis.

Comment.—Small quantities of scarlet red oil injected intraperitoneally caused no untoward symptoms, and the mixture was encysted as any other foreign body. When larger quantities of the oil or oil emulsion were injected, a general peritonitis followed. There was only local staining of the fat which came in contact with the oil. This material acted in the abdominal cavity as any other non-absorbable irritating powder would, and had no specific toxic effect.

Remarks.—Effect on General Health.—Feeding scarlet red, either in oil or dry, seemed to have no deleterious effect on the general health.

Absorption.—The absorption from the subcutaneous tissues was very slow. At the end of 30 days most of the oil injected could be found lying practically free in the subcutaneous tissues. There was very little, if any, absorption following intraperitoneal injections.

Thoracic Duct.—The receptaculum chyli of an animal who was fed 20 cubic centimeters of the oil solution one hour and a half before being sacrificed, showed a definite rose pink color. Four cubic centimeters of a pinkish milky fluid was easily obtained which immediately coagulated on exposure to the air. On allowing this to stand, minute red fat globules rose to the surface. Ether extract of this showed a pink color. No pink coloration was noted in the receptaculum chyli in any of the animals fed with the dry powder, even following an oil or fat diet.

Blood.—Ether extracts of the blood of animals fed with the oil solution or with dry powder were colorless. An animal fed for 9 weeks with daily average doses of 10 cubic centimeters of oil solution of scarlet red maintained 92 per cent hemoglobin (Sahli). This, with other observations, seemed to show that the hemoglobin was not appreciably diminished.

Muscle.—Ether extracts of heart muscle and diaphragm of dogs fed with the oil solution and also dry powder, was found to be colorless. There was no staining of the general muscular system either macroscopically or microscopically.

Glands.—The glandular system showed no coloration or change either macroscopically or microscopically.

Fat.—The body fat of both dogs and rabbits was universally stained when oil solution was used for feeding. The fat of an animal fed for 9 weeks was apparently no more deeply stained than that of animals fed for 9 days. The amount of the doses also seemed to have little effect on the intensity of the color, as apparently only a small amount of the oil solution was taken up. When dry powder was used the fat of the rabbits was universally stained, possibly a little less intensely than when the oil solution was used. On the other hand when dry powder was fed to dogs the body fat was very little stained. In some, not at all, and in others, the omental fat was a faint pinkish color, and the fat around the heart was a definite pink. This was especially noticeable when comparatively large amounts of the powder were fed in a short period of time. Microscopic examination of frozen sections of the deeply stained fat showed a diffuse pink stain with an occasional minute pink droplet between the cells. Subcutaneous injection of the oil solution, or oil emulsion, caused a staining of the subcutaneous fat immediately in the vicinity of the injected material. Intraperitoneal injection stained only the fatty tissue in the abdominal cavity where it came in contact with the oil solution. Neither of these injections caused staining of the body fat in general.

Feces and Urine.—Both the oil solution and the powder apparently passed through the intestine unchanged. Some of the oil was absorbed, from the intestine, but very little of the powder was taken up.

Throughout the experiments, even when large doses of the oil solution or dry powder was given, the animal showed no signs of diarrhea, except those which developed distemper. One of the dogs with distemper recovered, and although the feeding with the oil solution (15 cubic centimeters every other day) was kept up the animal's stools became firm and well formed. At no time were there found red blood corpuscles or mucus in the stools. The urine was unchanged throughout the experiments.

Bile.—The bile of some of the animals fed with oil solution was reddish brown in color, and, on shaking, the foam had a pinkish tinge. Ether and chloroform extracts showed a definite rose pink color.

In contrast to this, ether extracts of bile from dogs fed with dry powder showed no color.

Liver and Kidneys.—Sections showed no macroscopic or microscopic staining.

Effect on Intact Mucous Membranes.—The mucous membranes appeared normal in all the experiments. No proliferation of the mucosa of the gastro-intestinal tract was noted. The mucosa of the gall bladder and urinary bladder was unaffected.

Part II. Operative Experiments.

After a consideration of the results obtained in the preliminary experiments we concluded that the toxicity of the dyestuff used was a negligible quantity, and felt justified in proceeding with the operative experiments.

The stomach was chosen as the site of the operative defects

on account of its accessibility and also because of the prevalence of ulcers in this organ.

The question arose as to the method of producing an ulcer with a control of exactly the same size in another animal. Gastric ulcers may be produced in dogs by exhaustive bleeding and by feeding, over considerable periods of time, large doses of colon or diphtheria bacilli. It is needless to say that it was impossible to obtain ulcers having the desired requirements by the use of such methods.

It is a well known fact that defects made artificially in the gastric mucosa of dogs heal very rapidly. In spite of this we determined to make defects of the same size in both feeder and control, and to examine the specimens at varying intervals.*

Fifteen sets of experiments were done on thirty dogs. The age of the animals varied between four months and one year. Ether anesthesia was used in each experiment. All the animals were sacrificed under ether anesthesia.

Technic.—The part was shaved, washed with green soap and water, then with alcohol and ether. After the skin was thoroughly dry it was painted with tincture of iodin 2.5 per cent. The iodin solution was also freely used in the open wounds and after suture of the skin. Dry sterile gauze secured by a bandage was used wherever dressings were applied.

The selected area was outlined through a gastrotomy opening with a cutting punch, 1.5 centimeters in diameter, and this marked out portion was excised with sharp scissors. The defect in each instance was made quite close to the pylorus, and as far as possible in the same situation and of the same depth.

Catgut was used for closing the mucosa of the stomach, but everywhere else fine black silk was the suture and ligature material used.

In cutting the tissues for microscopic examination an area as close to the center of the ulcer as possible was selected.

For convenience we have divided the series into three groups. I. Those fed with the oil solution of scarlet red. II. Those fed with olive oil without scarlet red. III. Those fed with dry powder. To economize space we will report fully only one typical operation.

GROUP I. THOSE FED WITH ONE PER CENT SCARLET RED OIL.

Experiment 1.—Female, black and brown mongrel, about 1 year old.

Operation.—May 23, 1911. The stomach was brought up through an incision to the left of the mid-line, and a portion as near the pylorus as practicable was grasped in a stomach clamp. After packing off carefully, an incision was made through the stomach wall, and the sharp cutting punch was inserted and advanced, so as to mark out the area to be denuded as close to the clamp, and, consequently, as far from the incision as possible. Then this area, which was always clearly outlined, was manipulated so as to appear in the incision, and was then excised. (The depth of tissues removed varied, in some being only the mucous membrane, and in others the punch had cut down almost to the peritoneum.) The denuded area was then cauterized thoroughly with nitrate of silver stick, and allowed to fall back into its natural position.

The mucous membrane of the stomach was closed with catgut. The clamp was removed and the stomach wall was closed with a continuous inverting stitch. The outline of the defect, which could be seen through the stomach wall, was marked out on the surface with a circular suture of black silk. The stomach was dropped back. The abdominal wall was closed in layers. Dressed with dry gauze and bandage. Condition on leaving table excellent. *Per primam* healing.

May 25. Feeding begun with one per cent scarlet red oil solution; 20 cubic centimeters given. May 26: 10 cubic centimeters. May 27: 15 cubic centimeters. May 29: 20 cubic centimeters. May 31: 20 cubic centimeters. Total, 85 cubic centimeters. Mixed diet throughout the experiment.

June 1. Distemper. Animal sacrificed. *Autopsy.*—The conjunctivæ and mucous membranes were not colored. The skin showed no evidence of staining. The entire body fat was stained a rose pink. The thoracic duct contained a clear, colorless fluid. The bile was not examined. The urine was not colored. There had been no leakage from the stomach wound. On opening the stomach an unhealed ulcer 1.5 x .4 centimeters with overhanging edges was found. The floor was covered with granulation tissue. The contents of the lower portion of the small intestine and colon were colored red. The mucosa of the stomach and intestines appeared normal. There was no change made out in any of the other organs except the lung involvement due to distemper.

EXPERIMENT 1.—*Control.*—Male, black and tan mongrel, about 6 months old.

Operation.—May 23, 1911. A similar operation was performed, every detail corresponding as closely as possible to that above described. Condition on leaving the table excellent. *Per primam* healing.

June 1. Condition excellent. *Examination of specimen.*—There had been no leakage from the stomach wound. On opening the stomach an unhealed ulcer 1.3 x .5 centimeters was found. The walls rose less sharply than in the feeder and did not overhang the floor, which was of granulation tissue.

Histology.—(Dr. Sprunt.) Nine day ulcers. The scarlet red and control ulcers are approximately the same size in the sections, although the control goes somewhat deeper into the circular muscular coat.

Feeder.—The ulcer is not quite as deep as the control but the presence of an acute infection probably negatives this advantage. The floor is covered with a thick layer of polymorphonuclear leucocytes and necrotic tissue, into which there is growing from below an edematous granulation tissue, showing many polymorphonuclear leucocytes. The mucosa in all parts of the section is thick and extends out over the edge of the ulcer on each side, the redundant edges almost meeting in the mid-line. The sides of the ulcer are lined by a thin layer of epithelium, which also extends over the floor for a short distance, to a somewhat greater extent than in the control.

Control.—The sides and floor of the ulcer show very little necrotic material, but are lined by a thin layer of healthy granulation tissue. The mucosa throughout the section is thin and does not jut over the edges of the ulcer. There is a thin line of proliferating epithelium covering the sides and just beginning to extend over the floor. (Result, positive.)

EXPERIMENT 2.—Male, black and yellow hound, about 4 months old.

Operation.—June 6, 1911. Usual operation. Accidentally the sharp edge of the punch cut through the peritoneum at one point. This was turned in with a purse string suture. Condition on leaving the table excellent. *Per primam* healing.

June 8. Scarlet red oil feedings begun: 15 cubic centimeters given. June 10: 10 cubic centimeters. June 12: 15 cubic centimeters. June 13: 20 cubic centimeters. June 14: 10 cubic centimeters. June 16: 10 cubic centimeters. June 17: 20 cubic centimeters. Total, 100 cubic centimeters. Mixed diet throughout the experiment.

* We take this opportunity of expressing our thanks to Dr. T. P. Sprunt for the reports on the microscopic appearance of the ulcers, and gratefully acknowledge the aid of Dr. C. W. Rand for assisting us in carrying out the operative experiments.

June 20. Death from pneumonia. *Autopsy.*—The conjunctivæ and mucous membranes were not colored. The skin showed no evidence of staining. The entire body fat was stained a rose pink. The lungs showed lobar pneumonia. The thoracic duct contained a clear colorless fluid. The bile and urine were of normal color. There had been no leakage from the stomach wound. On opening the stomach a small healed ulcer was found. The walls of the depression rose quite sharply but did not overhang the floor. There was no scarlet red in the stomach or intestines, as there had been no feeding for three days. The mucosa of the stomach and intestines appeared normal. There was no change made out in any of the other organs.

Experiment 2.—*Control.* Male, black and brown mongrel, about 1 year old.

Operation.—June 6, 1911. Usual operation. Perforation duplicated and repaired. Condition on leaving the table excellent. *Per primam* healing.

June 20. Condition excellent. Animal sacrificed. *Autopsy.*—There had been no leakage from the stomach wound. On opening the stomach a healed ulcer was found, which was somewhat larger than that in the scarlet red animal. The walls of the ulcer shaded off gradually into the surrounding mucous membranes. This ulcer seemed definitely less advanced toward final healing than that in the feeder.

Histology.—(Dr. Sprunt.) Fourteen day ulcers. Sections are poor. In the control there is some doubt at first as to the site of the ulcer.

Feeder.—The healed ulcer is of larger extent and apparently of greater depth than in the control. The muscularis mucosa has disappeared, the submucosa shows dense granulation tissue with a considerable amount of brown pigment. The more superficial part of the circular muscle is replaced by this tissue. The mucosa covers the whole site and contains well developed, almost perfectly formed glands.

Control.—There is a large denuded area, near the surface of which is a silk suture with a considerable amount of reaction about it. There is, of course, an ulcer here, but the presence of the suture and the appearance of granulation tissue at corresponding points of the underlying coats of the stomach indicate that this is the site of the incision into the organ. Near this point there is an area without muscularis mucosæ, covered by epithelium, but with very poorly developed glands. The submucosa contains immediately beneath this point dense granulation tissue with many small round cells. The muscularis is not affected. (*Result*, positive.)

Experiment 3.—Male, white and yellow bull terrier, about 8 months old.

Operation.—June 8, 1911. Usual operation. Condition on leaving the table excellent. *Per primam* healing.

June 10. Scarlet red oil feedings begun, 10 cubic centimeters given. June 12: 15 cubic centimeters. June 13: 20 cubic centimeters. June 14: 10 cubic centimeters. June 16: 10 cubic centimeters. June 17: 20 cubic centimeters. June 20: 15 cubic centimeters. June 22: 15 cubic centimeters. June 23: 10 cubic centimeters. June 24: 15 cubic centimeters. June 26: 10 cubic centimeters. *Total*, 150 cubic centimeters. Mixed diet throughout the experiment.

June 27. Animal sacrificed, 18 hours after feeding. *Autopsy.*—The conjunctivæ and mucous membranes were not colored. The skin showed no evidence of staining. The entire body fat was stained a deep rose pink. The thoracic duct contained a clear colorless fluid. The bile was dark sherry color and showed a pinkish tinge in the foam, and red color in ether and chloroform extracts. The urine was not colored. There had been no leakage from the stomach wound. On opening the stomach a small healed ulcer measuring 4 x 1.5 millimeters and 2 millimeters deep was found. The mucosa forming the walls of the depression overhung the floor. The floor was puckered and of a pinkish color and seemed to be perfectly healed. There was a small amount of an oily red material smeared over the stomach mucosa, and definite scarlet red in the intestines. The mucosa of the stomach and intestines appeared normal. There was no change made out in any of the other organs.

Experiment 3.—*Control.* Female, white poodle, about 1 year old.

Operation.—June 8, 1911. Usual operation. Condition on leaving the table excellent. *Per primam* healing.

June 27. Animal sacrificed. *Autopsy.*—There had been no leakage from the stomach wound. On opening the stomach a healed ulcer 5 x 2.5 millimeters was found. The mucosa forming the walls rose less precipitously than in the feeder. The floor of the defect was more sharply defined, and was a grayish translucent color. Macroscopically the defect did not seem as perfectly healed as in the scarlet red animal.

Histology.—(Dr. Sprunt.) Nineteen day ulcers. This shows a picture similar to that in Experiment 2. Both ulcers are healed. They seem to have been of about the same size. The scarlet red ulcer is a little deeper than the control. While the difference is not as striking as in Experiment 2, the mucosa over the site of the ulceration in the scarlet red section is somewhat better formed than in the control. (*Result*, positive.)

Experiment 4.—Male, white and black pointer, about 1 year old.

Operation.—June 13, 1911. Usual operation. Condition on leaving the table excellent. *Per primam* healing.

June 14. Scarlet red oil feedings begun, 10 cubic centimeters given. June 16: 10 cubic centimeters. June 17: 20 cubic centimeters. June 20: 15 cubic centimeters. June 22: 15 cubic centimeters. Total, 70 cubic centimeters. Mixed diet throughout the experiment.

June 22. Animal sacrificed, 2 hours after feeding. *Autopsy.*—The conjunctivæ and mucous membranes were not colored. The skin showed no evidence of staining. The entire body fat was stained a rose pink color. There had been no leakage from the stomach wound. The thoracic duct contained a pinkish fluid. The bile and urine were of normal color. On opening the stomach a small unhealed ulcer was found with overhanging walls. There was scarlet red oil over the entire mucosa of the stomach and it was also found in the duodenum, in the sigmoid and rectum. The mucosa of the alimentary tract appeared normal. There was no change made out in any of the other organs.

Experiment 4.—*Control.* Male, yellow and white bull terrier, about 1 year old.

Operation.—June 13, 1911. Usual operation. Condition on leaving the table excellent. *Per primam* healing.

June 22. Animal sacrificed. *Autopsy.*—There had been no leakage from the stomach wound. On opening the stomach a small unhealed ulcer was found. The ulcer was slightly smaller in size than in the scarlet red animal.

Histology.—(Dr. Sprunt.) Nine day ulcers. Poor sections. Almost no difference to be noted. The mucosa edges of both jut over the ulcers unusually far. The scarlet red ulcer was somewhat deeper and perhaps has a slightly larger area of open ulcer not yet covered with epithelium. (*Result*, no difference.)

Experiment 5.—Female, black and brown mongrel about 1 year old.

Operation.—June 15, 1911. Usual operation. Condition on leaving the table excellent. *Per primam* healing.

June 16. Scarlet red oil feedings begun, 15 cubic centimeters given. June 17: 20 cubic centimeters. June 20: 15 cubic centimeters. June 22: 15 cubic centimeters. June 23: 10 cubic centimeters. June 24: 15 cubic centimeters. June 26: 10 cubic centimeters. June 27: 20 cubic centimeters. Total, 120 cubic centimeters. Mixed diet throughout the experiment.

June 27. Animal sacrificed, half hour after feeding. *Autopsy.*—

Conjunctivæ and mucous membranes were not colored. The skin showed no evidence of staining. The entire body fat was stained a rose pink. The thoracic duct contained a clear, colorless fluid. The bile was thick and resembled tincture of iodin in color. Ether extract showed a definite rose pink color. The urine was of normal color. There had been no leakage from the stomach wound. On opening the stomach a small healed ulcer was found. It was funnel-shaped and measured 3 x 4 millimeters, and was 2 millimeters deep. The mucosa forming the walls overhung the floor. The entire surface was found to be completely covered with red oil. Scarlet red could be seen as far down as the large intestine, as the animal was given some of the oil the night before. There were many active round worms in the intestine. The mucosa of the stomach and intestines appeared normal. There was no change made out in any of the other organs.

EXPERIMENT 5.—*Control.* Male, white fox terrier, about 1 year old.

Operation.—June 15, 1911. Usual operation. Condition on leaving the table excellent. *Per primam* healing.

June 27. Animal sacrificed. *Autopsy.*—There had been no leakage from the stomach wound. On opening the stomach an irregular unhealed ulcer, 8 x 3.5 millimeters, was found. The mucosa forming the walls did not overhang the floor as in the scarlet red animal. The floor was more sharply outlined and was covered with granulation tissue and mucus.

Histology.—(Dr. Sprunt.) Twelve day ulcers. The two ulcers seem to have been of about the same size and depth. The floor of each is formed by healthy granulation tissue which extends down to the circular muscle coat. In neither case does the mucosa hang over the edge of the ulcer. It is somewhat thicker in the scarlet red section. Epithelization is going on rapidly over each ulcer. The thin epithelial line covers the sides and all but the middle third of the floor of the control ulcer, while the whole floor has been covered in the scarlet red section. (*Result*, positive.)

Comment.—One feeder was sacrificed on account of distemper, one died of pneumonia, three were in good health when sacrificed.

In two the feedings were commenced the day after the operation, and in three, two days after operation. In two there were five feedings, and in three there were seven, eight and eleven feedings each.

The amount of one per cent oil solution given at a feeding varied between 10 and 20 cubic centimeters. The total amounts varied between 70 and 150 cubic centimeters.

In two instances the animals were fed just before being sacrificed.

The time elapsing between operation and examination of specimen was as follows: Nine days in 2 cases; 12 days in 1; 14 days in 1, and 19 days in 1.

The entire body fat was stained in each feeder. The staining was no deeper in the animal fed 150 cubic centimeters than when 70 cubic centimeters were given.

Scarlet red was demonstrated in the bile in two instances, one where the feeding was about 20 hours before death, and one where the feeding was 18 hours before death. In one instance it was not looked for, and in two none was found, this being without doubt due to the fact that the last oil feeding for this animal was two or three days before the examination was made. There was no change in the urine noted.

The mucosa of the alimentary canal, gall bladder and urinary bladder was normal in appearance.

The macroscopic and microscopic examination of the various organs and tissues showed no change due to the dyestuff.

The mucosa forming the walls of the defect, in several of the feeders, overhung the floor of the ulcer much more than in the controls.

Two of the feeders were in bad physicial condition during the latter portion of the treatment, but in spite of this the healing of the ulcer was further advanced in both of these than in the corresponding healthy controls.

The two nine day experiments showed unhealed ulcers. In Experiment 1, after feeding with 85 cubic centimeters, the ulcer was considerably more advanced toward healing than in the control. In this experiment there were five feedings, May 25, 26, 27, 29, and 31, which were begun two days after operation. The last feeding was the day before death.

The animal received the full benefit of the 85 cubic centimeters, which were given for three consecutive days, and then every other day for two feedings.

In the other nine day ulcer (Experiment 4), there were five feedings, June 14, 16, 17, 20, and 22, which were begun the day after operation. The last feeding was two hours before death, thus the animal received the benefit of only 55 cubic centimeters of the 70 cubic centimeters given. The feedings were less regular than in the other nine day experiment, and very little difference could be noted in the appearance of the ulcer in the feeder and in the control. The difference in the advancement of healing in Experiment 1 and Experiment 4 can possibly be explained by the fact that more of the oil solution was given in Experiment 1, and the feedings were at more favorable intervals.

The twelve, fourteen and nineteen day ulcers, in the feeders, were all healed. The twelve day control was unhealed. The fourteen and nineteen day controls were healed, but the mucosa was not as well developed as in the feeders.

In summing up the results of this group there is no doubt that the animals fed with the oil solution showed more advanced healing of the ulcers in four instances than in the corresponding controls. In one instance, where 55 cubic centimeters of the oil were given, the feeder and control were equally far advanced toward healing. So, from the above, we may conclude that in four out of five experiments the epithelium of the ulcer edges was stimulated considerably more in the animals fed with the oil solution than in the controls.

GROUP II. THOSE FED WITH PURE OLIVE OIL.

In order to determine whether the scarlet red or the olive oil caused the epithelial stimulation in the first group of experiments, a second set was undertaken, in which pure olive oil was used for the feeding. The details of the first set of experiments were duplicated as far as possible.

EXPERIMENT 6.—Female, black mongrel, about 14 months old.

Operation.—May 27, 1912. Usual operation. Condition on leaving the table excellent. *Per primam* healing.

May 29. Feeding with pure olive oil begun. The amounts and intervals between the feedings corresponded to those in Experiment 1. Mixed diet throughout the experiment.

June 5. Animal sacrificed. *Autopsy.*—There had been no leak-

age from the stomach wound. On opening the stomach a small unhealed ulcer with overhanging edges was found.

EXPERIMENT 6.—*Control.* Male, yellow mongrel, about 7 months old.

Operation.—May 27, 1912. Usual operation. Condition on leaving the table excellent. *Per primam* healing.

June 5. Animal sacrificed. *Autopsy.*—There had been no leakage from the stomach wound. On opening the stomach an unhealed ulcer was found. The mucosa edges did not overhang the base as markedly as in the feeder.

Histology.—(Dr. Sprunt.) Nine day ulcers. There is an ulcer in each section undergoing healing with a granulation tissue floor which involves in each case the circular muscle coat of the stomach. The ulcer in the control section is deeper and considerably larger than in the feeder. Both ulcers are infected, especially the control whose floor is covered by masses of polymorphonuclear leucocytes. The superficial portion of the granulation tissue forming the floor of the ulcer shows many widely dilated and engorged capillaries, and the interstices of the tissue are filled with polymorphonuclear leucocytes. The mucosa overhangs the edges of the ulcer a little, and the line of epithelium has grown out for a short way across the floor of the ulcer. The mucosa in the feeder overhangs the ulcer to a marked extent, with two mucosal edges almost meeting each other. The uncovered floor of the ulcer is much smaller than in the control section. The acute inflammation is less and the ulcer seems smaller in every dimension. (*Result*, healing further advanced in feeder.)

EXPERIMENT 7.—Male, yellow mongrel, about 11 months old.

Operation.—May 27, 1912. Usual operation. Condition on leaving the table excellent. *Per primam* healing.

May 29. Feedings with pure olive oil begun. The amounts and intervals between the feedings corresponded to those in Experiment 2.

June 10. Animal sacrificed. *Autopsy.*—There had been no leakage from the stomach wound. On opening the stomach a healed ulcer 9 x 1 millimeters was found.

EXPERIMENT 7.—Control. Male, black and white fox terrier, about 7 months old.

Operation.—May 27, 1912. Usual operation. Condition on leaving the table excellent. *Per primam* healing.

June 10. Animal sacrificed. *Autopsy.*—There had been no leakage from the stomach wound. On opening the stomach an ulcer 5 x 2 millimeters was found, which was nearly healed.

Histology.—(Dr. Sprunt.) Fourteen day ulcers. The ulcer in neither section involves the circular muscle. It extended in each into the submucosa. In the section marked feeder, the ulcer is covered not only by epithelium but by mucosa in large part. A small area in the center is covered by a line of epithelium only. Beneath this area the granulation tissue contains a few polymorphonuclear leucocytes. In the control section the ulcer seems wider. The mucosa has extended over the edges of the ulcer, but in the center there is perhaps one-fourth of its extent uncovered by epithelium. The granulation tissue forming this portion of the floor shows quite a number of polymorphonuclear leucocytes. (*Result*, healing further advanced in the feeder.)

EXPERIMENT 8.—Female, black and brown hound, about 8 months old.

Operation.—May 28, 1912. Usual operation. Condition on leaving the table excellent. *Per primam* healing.

May 30. Feeding with pure olive oil begun. The amounts and intervals between the feedings corresponded to those in Experiment 3.

June 16. Animal sacrificed. *Autopsy.*—There had been no leakage from the stomach wound. On opening the stomach a small depression measuring 4 x 2 millimeters marked the site of the healed ulcer.

EXPERIMENT 8.—*Control.* Male, black mongrel, about 8 months old.

Operation.—May 28, 1912. Usual operation. Condition on leaving the table excellent. *Per primam* healing.

June 16. Animal sacrificed. *Autopsy.*—There had been no leakage from the stomach wound. On opening the stomach a small depression measuring 2 x 3 millimeters marked the site of the healed ulcer.

Histology.—(Dr. Sprunt.) Nineteen day ulcers. The ulcers in the two sections seem to have been of about equal extent and are now both healed. The scar tissue is fairly dense in each, and covered in both cases by mucosa. There is no marked difference in the control and the feeder. (*Result*, equally well healed.)

EXPERIMENT 9.—Male, white fox terrier, about 9 months old.

Operation.—May 29, 1912. Usual operation. Condition on leaving table excellent. *Per primam* healing.

May 29. Feeding with pure olive oil begun. The amounts and intervals between the feedings corresponded to those in Experiment 4.

June 6. Animal sacrificed. *Autopsy.*—There had been no leakage from the stomach wound. On opening the stomach a small, unhealed ulcer was found.

EXPERIMENT 9.—*Control.* Female, black and brown mongrel, about 7 months old.

Operation.—May 29, 1912. Usual operation. Condition on leaving the table excellent. *Per primam* healing.

June 6. Animal sacrificed. *Autopsy.*—There had been no leakage from the stomach wound. On opening the stomach a small, apparently healed ulcer was found.

Histology.—(Dr. Sprunt.) Nine day ulcers. In the feeder section the ulcer is deeper, extending into the circular muscle coat. The mucosa overhangs each edge and a line of epithelium has grown along the sides and floor of the ulcer, but leaves about one-half its surface uncovered. This portion is covered by a layer of mucus containing many polymorphonuclear leucocytes. The granulation tissue forming the floor of the ulcer is also full of polymorphonuclear leucocytes. The ulcer in the control section seems to have involved the muscle coat less than in the other. The ulcer is completely covered by epithelium. (*Result*, healing further advanced in the control.)

EXPERIMENT 10.—Male, white and black mongrel, about 8 months old.

Operation.—May 28, 1912. Usual operation. Condition on leaving the table excellent. *Per primam* healing.

May 29. Feeding with pure olive oil begun. The amounts and intervals between the feedings corresponded to those in Experiment 5.

June 9. Animal sacrificed. *Autopsy.*—There had been no leakage from the stomach wound. On opening the stomach a nearly healed ulcer 2 x 4 millimeters was found.

EXPERIMENT 10.—*Control.* Female, black and white mongrel, about 5 months old.

Operation.—May 28, 1912. Usual operation. Condition on leaving the table excellent. *Per primam* healing.

June 9. Animal sacrificed. *Autopsy.*—There had been no leakage from the stomach wound. On opening the stomach an unhealed ulcer 4 x 9 millimeters was found.

Histology.—(Dr. Sprunt.) Twelve day ulcers. Comparison of the two sections in this set seems hardly fair. The ulcer in the feeder section extended to the circular muscle layer, and has been almost completely covered by epithelium. The ulcer in the control section went through both muscular layers and extended to the serosa. The mucosa overhangs each edge to a considerable extent. The sides of the ulcer are lined by granulation tissue, and the floor contains mucus, many polymorphonuclear leucocytes, and eosin staining hyaline material, suggestive of necrotic tissue. There has been a remarkable proliferation of the peritoneal

cells forming a thick node opposite the ulcer, and virtually preventing its perforation. This node of cells consists of anastomosing columns of polyhedral cells with a slight tendency toward a foamy protoplasm. There are capillaries here and there between the cells. At the basal portion of the node granulation tissue may be seen extending in between the columns of cells. The picture suggests that of adrenal cortex. (*Result*, healing further advanced in the feeder.)

Comment.—All of the feeders were in good health when sacrificed. The amounts of oil and the intervals between the feedings corresponded as closely as possible to those in Group I.

The fourteen and nineteen day ulcers in the feeders were healed. Both nine day ulcers and the twelve day ulcers in the feeders were unhealed. The controls in the nineteen day and nine day (Experiment 9) ulcers were healed. The rest were unhealed.

In comparing the epithelial stimulation in the feeder in Experiment 1, with its duplicate in Experiment 6, we note that there is greater stimulation of epithelium from the edges of the ulcer in the animal fed with scarlet red oil, than in the animal fed with pure olive oil.

Experiment 2, compared with Experiment 7. The development of the mucosa was much further advanced in the animal fed with scarlet red oil than in the olive oil fed animal.

Experiment 3, compared with Experiment 8. The mucosa over the ulcer was better developed in the animal fed with the scarlet red oil, than in the olive oil fed animal.

Experiment 4, compared with Experiment 9. There was little if any difference in the extent of epithelial stimulation in these two ulcers. This condition was not unexpected in these two experiments.

Experiment 5, compared with Experiment 10. The epithelial stimulation was greater in the animal fed with scarlet red oil than in the olive oil fed animal.

In Experiments 1 and 3 the size and appearance of the control ulcers were about the same as in their duplicate controls in Experiments 6 and 8.

In Experiments 2 and 5 the controls were further advanced toward healing than in their duplicate controls in Experiments 7 and 10.

In Experiment 4 the control was not so far advanced toward healing as its duplicate control in Experiment 9.

In summing up the results in this group, we find that in three instances the feeders in the animals fed with the olive oil showed more advanced healing than in the corresponding controls. In one instance the feeder and the control were equally far advanced toward healing, and in one the control was further advanced toward healing the feeder.

Now, when we compare the advancement of healing in the feeders in Group I, with those in Group II, we find that in four out of five instances the epithelial stimulation was much more marked in the animals fed with scarlet red oil, than in those fed with pure olive oil.

Although these experiments are very few in number they seem to show that there is a definite stimulation of the epithelium of the gastric mucosa caused by the scarlet red in oil, which is not caused by the olive oil alone.

GROUP III. THOSE FED WITH DRY POWDER, IN CAPSULES.

EXPERIMENT 11.—Female, black and white fox terrier, about 6 months old.

Operation.—December 28, 1911. Usual operation. Condition on leaving the table excellent. *Per primam* healing.

December 29. Feeding with scarlet red powder begun: a.m., 1 gram; p. m., .8 gram. December 30: a. m., .8 gram; p. m., .8 gram. December 31: a. m., .8 gram. January 1, 1912: a. m., 1.6 grams. January 2: a. m., 1.6 grams; p. m., 1.6 grams. January 3: a. m., 1.6 grams; p. m., 1.6. grams. Total: 12.2 grams. Mixed diet throughout the experiment.

January 4, 1912. Death from pneumonia. *Autopsy.*—The conjunctivæ and mucous membranes were not colored. The skin showed no evidence of staining. The entire body fat of this animal was stained a rose pink. This can be accounted for by the fact that 1 gram of scarlet red in oil emulsion had been given the day of operation, before the dry powder was begun. The thoracic duct contained a colorless fluid. The bile and urine were of normal color. There had been no leakage from the stomach wound. On opening the stomach a small unhealed, funnel-shaped ulcer was found. The mucosa forming the walls overhung the floor, which was of granulation tissue. There was no scarlet red in the stomach, but it was plentiful in the ileum and lower bowel. The mucosa of the stomach and intestines appeared normal. No change worthy of note was made out in any other organ or tissue.

EXPERIMENT 11.—*Control.* Male, black and white fox terrier, about 1 year old.

Operation.—December 28, 1911. Usual operation. Condition on leaving the table excellent. *Per primam* healing.

January 4, 1912. Animal sacrificed. *Autopsy.*—There had been no leakage from the stomach wound. On opening the stomach an oblong unhealed ulcer was found, which was larger but not so deep, as the ulcer in the feeder, although it seemed more nearly healed. The walls of the ulcer did not overhang the floor as much as in the feeder.

Histology.—(Dr. Sprunt.) Seven day ulcers. The ulcers in the sections are of about the same size, but the scarlet red ulcer is deeper than the control, hence the comparison is not altogether fair. The control ulcer is covered almost entirely with epithelium, and there is beginning regeneration of the mucosa in the middle of the ulcer's floor. There is much mucus. In the scarlet red section new formed mucosa hangs over at both edges, but there is no growth of epithelium over the floor of the ulcer, which is formed of granulation tissue. Mitosis is not marked in either of the sections. (*Result*, negative.)

EXPERIMENT 12.—Female, black and yellow mongrel, about 1 year old. Small animal.

Operation.—January 2, 1912. Usual operation. A perforation of considerable size was accidentally made through the stomach wall by the sharp punch, and was immediately sutured. Condition on leaving the table excellent. *Per primam* healing.

January 3. Feeding with scarlet red powder begun: a. m., .9 gram; p. m., .9 gram. January 4: a. m., 1.6 grams; p. m., 1.6 grams. January 5: a. m., 1.6 grams; p. m., 1.6 grams. January 6: a. m., 1.6 grams; p. m., 1.6 grams. January 8: a. m., 2 grams; p. m., 2 grams. January 9: a. m., 2 grams; p. m., 1.6 grams. January 10: a. m., 2 grams; p. m., 1.6 grams. January 11: a. m., 1.6 grams; p. m., 1.6 grams. January 12: a. m., 1.6 grams; p. m., 1.6 grams. January 13: a. m., .8 gram; p. m., .8 gram. January 14: a. m., 1.6 grams. January 15: a. m., .8 gram; p. m., .8 gram. January 16: a. m., .8 gram; p. m., .8 gram. January 17: a. m., .8 gram; p. m., .8 gram. January 18: a.m., .8 gram; p. m., 1.6 grams. January 19: a. m., 1.6 grams; p. m., 1.6 grams. January 20: a. m., 1.6 grams; p. m., 1.6 grams. *Total*, 47.7 grams. Mixed diet throughout the treatment.

January 20. Death, from distemper. *Autopsy.*—The conjunctivæ and mucous membranes were not colored. The skin showed

no evidence of staining. There was no visible staining of the body fat. The thoracic duct contained a colorless fluid. The bile and urine were of normal color. There had been no leakage from the stomach wound. On opening the stomach a small, funnel-shaped healed ulcer with overhanging walls was found. The floor was apparently covered with mucus. The mucous membranes of the stomach and intestines were normal. Scarlet red was present everywhere in the stomach and intestines. There was no change made out in any of the other organs due to the dyestuff.

EXPERIMENT 12.—*Control.* Female, black and white mongrel, about 1 year old.

Operation.—January 2, 1912. Usual operation. No perforation was made. Condition on leaving the table excellent. *Per primam* healing.

January 20. Animal sacrificed. *Autopsy.*—There had been no leakage from the stomach wound. On opening the stomach a shallow, healed ulcer was found, whose walls did not overhang the floor.

Histology.—(Dr. Sprunt.) Nineteen day ulcers. The comparison here is not entirely fair, since, from the sections, one would at once say that the scarlet red ulcer was of considerably greater depth originally than in the control. It extends into the muscle which under the site of ulceration is infiltrated with granulation tissue throughout most of the circular coat. The site is completely covered with epithelium, but the mucosa is thin and manifestly imperfect. The control ulcer must have been comparatively shallow. The muscle is unaffected. The muscularis mucosa is interrupted for a very short distance and beneath this the submucosa is infiltrated with very vascular granulation tissue, the capillaries of which are widely distended. The mucosa over the site of the ulcer is of about normal thickness and appearance. (*Result*, negative.)

EXPERIMENT 13.—Male, black and tan mongrel, about 4 months old.

Operation.—January 11, 1912. Usual operation. Condition on leaving the table excellent. *Per primam* healing.

January 12. Feeding with scarlet red powder begun: a. m., 1.6 grams; p. m., 1.6 grams. January 13: a. m., .8 gram; p. m., .8 gram. January 14: a. m., .8 gram; p. m., .8 gram. January 15: a. m., .8 gram; p. m., .8 gram. January 16: a. m., .8 gram; p. m., .8 gram. January 17: a. m., .8 gram; p. m., .8 gram. January 18: a. m., .8 gram; p. m., .8 gram. January 19: a. m., 1.6 grams; p. m., 1.6 grams. January 20: a. m., 1.6 grams; p. m., 1.6 grams. January 21: a. m., 2 grams. January 22: a. m., 2 grams. *Total* 23.2 grams. Mixed diet throughout the experiment.

January 22. Animal sacrificed. *Autopsy.*—The conjunctivæ and mucous membranes were not colored. The skin showed no evidence of staining. The omental fat was stained a faint rose pink. Over the stomach incision and over the heart, the fat was found to be quite deeply stained. Scarlet red was found in the stomach and in the intestines, as the dog had been fed just before being sacrificed. The thoracic duct contained a colorless fluid. The bile and urine were of normal color. There had been no leakage from the stomach wound. On opening the stomach a small deep unhealed ulcer with overhanging walls was found. The floor was covered with granulation tissue. There was considerable puckering around the defect. The mucosa of the stomach and intestines otherwise was unchanged. There was no change worthy of note in the other organs or tissues.

EXPERIMENT 13.—*Control.* Female, black and yellow mongrel, about 9 months old.

Operation.—January 11, 1912. Usual operation. Condition on leaving the table excellent. *Per primam* healing.

January 22. Animal sacrificed. *Autopsy.*—There had been no leakage from the stomach wound. On opening the stomach a small, perfectly healed ulcer was found. The defect was not quite as deep as that in the feeder, and the walls did not overhang so much.

Histology.—(Dr. Sprunt.) Twelve day ulcers. In these sections the ulcers are of about the same size and depth, extending into the submucosa, which beneath the ulcer shows the usual cellular granulation tissue. Possibly the scarlet red ulcer is a little the deeper. The control ulcer is covered with epithelium, and proliferation has gone on to partial reformation of the mucosa. The scarlet red ulcer shows overhanging mucosa edges, but the floor of the ulcer is covered at the edges only, leaving a larger central portion denuded. The mucosa in the two sections is not of the same type, suggesting that the ulcers were not made at exactly corresponding points in the two stomachs. In the control the mucosa is thicker throughout, and contains many acid cells. In the scarlet red section it is thinner, composed of more simple tubular glands, with no acid cells, apparently nearer the pylorus. (*Result*, negative.)

EXPERIMENT 14.—Male, black and white fox terrier, about 1 year old.

Operation.—January 23, 1912. Usual operation. Condition on leaving the table excellent. *Per primam* healing.

January 23. Feeding with scarlet red powder begun: a. m., 2 grams. January 24: a. m., 2 grams; p. m., 2 grams. January 25: a. m., 2 grams; p. m., 2 grams. January 26: a. m., 2 grams; p. m., 2 grams. *Total*, 14 grams. Mixed diet throughout the experiment.

January 27. Animal sacrificed. *Autopsy.*—The conjunctivæ and mucous membranes were not colored. The skin showed no evidence of staining. The body fat was not stained. The thoracic duct contained a colorless fluid, and the bile and urine were of normal color. There had been no leakage from the stomach wound. On opening the stomach a small, deep, unhealed ulcer with overhanging walls was found. The floor was of granulation tissue. The mucous membranes of the stomach and intestine were normal. Scarlet red was found in the ileum and colon. There was no change made out in any of the other organs or tissues.

EXPERIMENT 14.—*Control.* Male, black and white fox terrier, about 1 year old.

Operation.—January 23, 1912. Usual operation. Condition on leaving the table excellent. *Per primam* healing.

January 27. Animal sacrificed. *Autopsy.*—There had been no leakage from the stomach wound. On opening the stomach an ulcer of considerably larger size than in the feeder, was found. Its floor was infected, and was covered with an inflammatory exudate.

Histology.—(Dr. Sprunt.) Five day ulcers. The scarlet red sections show less infection, but the ulcer is deeper than in the control, going through all of the muscle and separated from the peritoneum by granulation tissue. New formed mucosa overhangs each edge. A line of epithelium lines the sides and a very small part of the base. Mitoses are more numerous than in the control. The control ulcer extends well into the muscular coat. There is conspicuous acute inflammatory exudate in the floor of the ulcer and in the submucosa around it. This extends also through the muscular coat to the peritoneum where there is an organising peritonitis. A small amount of new mucosa has formed and jutted out slightly at each edge. There is a slight growth of epithelium over the base at one end. On account of the acute infection in the control a comparison seems unfair, but perhaps the increased depth of the ulcer in the scarlet red section may tend to neutralise the acute infection in the control. (*Result*, positive.)

EXPERIMENT 15.—Male, black mongrel, about 1 year old.

Operation.—January 31, 1912. Usual operation. Condition on leaving the table excellent. *Per primam* healing.

January 31. Feeding with scarlet red powder begun: p. m., .8 gram. February 1: a. m., 2 grams. February 2: a. m., 1.6 grams; p. m., 1.6 grams. February 3: a. m., 1.6 grams; p. m., 1.6

grams. February 5: a. m., 1.6 grams; p. m., 1.6 grams. February 6: a. m., 1.6 grams; p. m., 1.6 grams. *Total*, 15.6 grams. Mixed diet throughout the experiment.

February 7. Animal sacrificed. *Autopsy.*—The conjunctivæ and mucous membranes were not colored. The skin showed no evidence of staining. The omental fat was a very faint pink, but the body fat was not stained. The thoracic duct contained a colorless fluid, and the bile and urine were of normal color. There had been no leakage from the stomach wound. On opening the stomach a small, deep, unhealed ulcer was found. The edges overhung so as to nearly conceal the defect. The mucous membrane of the stomach and intestine was normal. Scarlet red was found in the stomach, ileum and colon. No change was made out in any of the other organs or tissues.

EXPERIMENT 15.—*Control.* Male, yellow mongrel, about 1 year old.

Operation.—January 31, 1912. Usual operation. Condition on leaving the table excellent. *Per primam* healing.

February 7. Animal sacrificed. *Autopsy.*—There had been no leakage from the stomach wound. On opening the stomach an unhealed ulcer was found, which was larger than that in the feeder. The walls did not overhang so much.

Histology.—(Dr. Sprunt.) Seven day ulcers. Feeder. The ulcer extends into the muscle, but not as deeply as in the control. The floor is formed by granulation tissue. Epithelium covers the floor of the ulcer in a thin line, except for the middle third. The mucosa is redundant on both sides almost meeting in the mid-line, over the ulcer. Mitotic figures are more numerous than in the control.

Control.—Ulcer extends into the muscular coat. The floor of the ulcer is formed by a thick mass of necrotic tissue with many polymorphonuclear leucocytes. Beneath this there is a layer of granulation tissue. The proliferating epithelium lines both sides. On the floor there is only a short strip at one end. (*Result*, positive.)

Comment.—One feeder died of pneumonia, and one of distemper. Three were in good health when sacrificed. In two the feeding was begun the day of operation, and in three the day after operation. In two there were ten feedings, and in three there were seven, twenty and thirty-three feedings each. Morning and evening feedings were resorted to in each experiment, in order to keep the scarlet red powder in the stomach over as long a period as possible.

The amount of dry powder given at a feeding varied between .6 and 2 grams. The greatest amount given in a single day was 4 grams. The total amount varied between 12.2 and 47.7 grams.

In one experiment the animal died of distemper a few hours after the last feeding. In one the animal was sacrificed two hours after feeding. In both of these scarlet red was abundant in the stomach. In three where the feeding was the evening before the examination of the specimen, no scarlet red was found in the stomach. The time elapsing between operation and examination of the specimen was as follows: Seven days in 2 cases, 5, 12, and 19 days in one each.

The entire body fat was stained in one animal, as 1 gram of the powder in oil emulsion had been given before the feeding with dry powder was commenced. In two the omental fat, and the fat around the heart, was stained a faint pink, and in two there was no staining whatever.

Scarlet red was not demonstrated in the bile in any animal fed with dry powder.

There was no change in the urine noted.

The mucosa of the alimentary canal, gall bladder, and urinary bladder was normal in appearance.

The macroscopic and microscopic examination of the various organs and tissues showed no change due to the dyestuff.

The mucosa forming the walls of the defect in all but one of the feeders overhung the floor of the ulcer much more than in the controls.

The two 7 day experiments showed unhealed ulcers. In one (Experiment 11), after feeding 12.2 grams in six days there was practically no epithelial growth over the floor of the ulcer, although the ulcer was distinctly smaller, but deeper than the control. The control was nearly covered with epithelium.

In the other 7 day ulcer (Experiment 15), after feeding 15.6 grams in six days, the epithelial growth was considerably more advanced in the feeder than in the control, and the ulcer in the feeder was smaller, but deeper, than the control.

Perhaps the difference in epithelial stimulation might be due to the fact that in Experiment 11 the health of the animal was bad after the first two days, and death followed from pneumonia.

The five day ulcer in the feeder was further advanced toward healing than the control. The twelve day ulcer in the control was healed, while the feeder was not so far advanced toward healing. The nineteen day ulcers were both healed, but the mucosa in the control was developed to a greater extent.

In summing up the results of this group of experiments it will be seen that in three out of five sets of animals the controls were further advanced toward healing than the feeders. In other words feeding with the dry dyestuff did not give the same favorable results noted in Group I, although very much more of the material was introduced into the stomach. The larger amounts seem to be more than counterbalanced by the length of time the oil solution remained in contact with the defect in the stomach mucosa.

This group again demonstrates the non-toxicity of the dyestuff, which can be noted on glancing over the amounts fed in a comparatively short time. All the animals were small, and the doses were very large when the body weight was taken into consideration.

Remarks.—In Group I (fed with scarlet red oil solution), the defects made artificially in the feeders were further advanced toward healing, than in the corresponding controls, in four out of five instances.

In Group II (fed with pure olive oil), similar defects in the feeders were further advanced, than in the corresponding controls, in three out of five instances.

Comparing the advancement of the healing in the feeders in the duplicate experiments in these two groups, we find that the epithelial stimulation was more marked in those animals fed with the scarlet red oil solution than in those fed with pure olive oil.

In Group III (fed with dry powder), similar defects in the feeders were further advanced toward healing, than in the corresponding controls, in only two out of five instances.

The lack of epithelial stimulation may be due to the fact

that the feedings were too far apart to keep the material in contact with the denuded area. This objection could be obviated by giving the doses at short intervals.

In several instances the scarlet red oil solution was found smeared over the entire mucosa of the stomach, as long as 18 hours after feeding, and this suggests that the dyestuff administered in this way might stay in contact with the mucosa continuously if given at the proper intervals.

Both the powder and the oil solution were in actual contact with the denuded surfaces in every instance where an examination was made before the dyestuff had passed on into the intestine.

The stimulating effect of scarlet red on epithelium in other situations is well authenticated, so we may at least surmise that it probably had a similar stimulating effect on the epithelium in these experiments. The best results of local use of scarlet red in hastening epithelial stimulation is obtained when it is applied in an oil solution, or in a lanolin or vaseline base, and it seems probable that the most satisfactory effects in such a situation as the stomach, would be obtained when it was given in an oily solution.

We were able to examine the subcutaneous fat of two patients, one of whom had taken internally 32 grams, and the other 63.3 grams, of the dry powder within four weeks, and there was no staining of the fat. Another patient, who had been given 66.5 grams of the powder in less than four weeks, was operated on several weeks later for another trouble, and there was no staining of the subcutaneous or omental fat.

Whether the oil solution or an oil emulsion taken internally will stain human fat, we are not, as yet, prepared to say.

The use of the oil solution in treating patients might be contraindicated on account of the staining of the fat, but there is no experimental evidence of either conjunctivæ or skin being visibly stained pink. The fact that the stain is gradually eliminated is also to be borne in mind, as, if the oil solution is found to give the best clinical results, the stain will eventually disappear from the fat.*

* In order to avoid staining the skin, bed clothes, etc., it seems advisable to administer the dyestuff in a container of some sort. We might suggest that if the powder is to be used it should be given in small doses, say 5 grains every 3 or 4 hours, in capsules, in order to keep it continuously in the stomach. If the oil solution is to be given, a flexible gelatin capsule containing 4 or 5 cubic centimeters each might be given.

In none of the experiments has there been any tendency noted to the overgrowth of mucosa of the alimentary canal, and from our experience with the stimulating effect of scarlet red on epithelium in other situations, we feel that there is no more danger of producing a malignant degeneration in an ulcerated area of the stomach, than if the ulcer were properly treated by any other method. That is, medically for a reasonable time, say about six weeks, or two months, and then, unless there is definite relief of all symptoms, the case should become surgical.

In the treatment of gastric ulcer in the human a certain amount concerning the efficacy of a method can be told by the alleviation of the symptoms, but the only way to definitely determine the beneficial action of scarlet red in the treatment of these cases is to have a series of patients with all the symptoms and signs of gastric ulcer, and who would ordinarily be passed over to the surgeon, receive this treatment for several weeks, before coming to operation.

Conclusions.

The dyestuff used in this series of experiments is not toxic and apparently has no deleterious effect on either dogs or rabbits.

When given by mouth it is a fat selecting vital stain. In the course of months the stain is gradually eliminated.

Subcutaneous and intraperitoneal injections stain only the fat in actual contact with the scarlet red oil solution.

It is difficult to say from these few operative experiments whether the scarlet red has, or has not, a definite stimulating action on the epithelium of defects in the gastric mucosa. However, the scarlet red oil solution caused a more rapid and better developed growth of epithelium in the group in which it was used, than occurred in the duplicate group where plain olive oil was used.

The results with dry powder were not so favorable experimentally, but this may have been due to the fact that the material was not continuously in contact with the denuded area.

We were unable to determine the relative effect of the scarlet red on chronic gastric ulcers, as it was impossible to produce chronic ulcers in dogs with controls of exactly the same size.

Our experiments are suggestive, and, as this dyestuff may be safely administered, we feel that it is worthy of a thorough clinical trial.

SUBLUXATION OF THE MAJOR CORNU OF THE HYOID BONE (DYSPHAGIA VALSALVIANA).

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The rarity of subluxation of the major cornu of the hyoid bone, or the infrequent diagnosis of this condition, explains why so few cases have been reported. The writer's attention was attracted to this fact when he was trying to discover cases with similar symptoms to those which a patient had who presented himself for diagnosis in the Laryngological Dispensary of The Johns Hopkins Hospital.

The patient, Dr. McC——, of Texas, stated that in 1887, when a child of seven years, he suddenly became unable to swallow. He was taken by his father to a physician who tried

in vain to get something into place in his neck which had apparently become "twisted." The longer the condition persisted the more painful were his efforts to swallow.

After two days, during which time the child remained with the physician, there was a sudden restoration of the normal condition. Repeatedly, after this, he had similar attacks in which swallowing became at first painful and then impossible. They would come on when he yawned or turned his head suddenly. Sometimes the condition would be relieved of itself, as in the first attack, and sometimes he was able to obtain relief by pulling hard on the skin in front of the sterno-mastoid muscle. At the age of twenty-three he learned to "set it" as he expressed it. He inserts his index finger into his mouth at the side and base of the tongue at a point which corresponds, when one feels on the outside, to the attachment of the major cornu of the hyoid bone to the superior cornu of the thyroid cartilage, and presses outward and forward. Something goes back into position with a distinct click. These points were determined on examination during the time in which the abnormal condition was present. As far as could be determined by a laryngoscopical examination there was no change in the larynx.

A study of the anatomical relations of the hyoid bone and of the symptomatology of eleven cases of subluxation of the major cornu of the hyoid bone, including the author's case and ten cases collected from the literature, makes it seem probable that in this case there was a loose articulation of the major cornu with the body of the hyoid bone, or a loose attachment of the tip of the major cornu to the superior horn of the thyroid, allowing greater freedom of movement of the major cornu than is normally present.

I will give only a brief description of the topographical anatomy. The hyoid bone lies in most intimate relation to the larynx above and the tongue below. It is the principal support of the tongue through its muscular and ligamentous attachments, and it is associated with all the movements of the larynx by ligaments which unite it to the thyroid cartilage. The attachment of the major cornu of the hyoid bone to the superior cornu of the thyroid cartilage through the medium of the lateral thyro-hyoid ligament may be loose or firm according to the degree of tension of this ligament. The attachment of the major cornu to the body of the hyoid, sometimes osseous in advanced age, is at other times the site of a true joint containing a synovial membrane.

Olivier D'Angers,[1] in 1837, mentioned four cases of the above condition which he had collected from the literature; the first was observed by Valsalva, in which dysphagia followed the ingestion of a hard and voluminous body, and which he attributed to the dislocation of the cartilaginous appendices of the hyoid bone. The article swallowed was a piece of meat. Valsalva reduced this dislocation by pressing with his fingers at the back of the mouth. D'Angers quotes Sauvage as naming the condition dysphagia valsalviana.

The second and third cases, reported by P. B. Molinelli,[2] are as follows:

A young student of slight build was grasped violently by the throat by a much stronger man, and, in the struggle which ensued, pressure was made on the right external part of the neck. It became at once impossible for him to swallow either liquids or solids, however hard he tried. Molinelli saw him one hour after the assault; he was in a state of extreme anxiety; a cold and abundant sweat covered his whole body; his pulse was small; he seemed in danger of imminent dissolution. However, his articulation and respiration were very little altered. No deformity was noticed in the region of the larynx, but between this organ and the right sterno-mastoid muscle, there was a tumor acutely painful to the slightest pressure.

Molinelli's treatment consisted in having the patient's head held firmly while he introduced his right index finger between the right tonsil and the base of the tongue, at the same time applying the index and middle fingers of his left hand to the outer side of the neck in the region occupied by the hyoid bone. Then with the finger in the back of the mouth, the right great cornu of the hyoid bone was pushed gradually outward while the fingers placed at the outside of the neck limited and directed this pressure. This maneuver had scarcely been executed when the patient felt relieved and was able to swallow a little water. The maneuver was immediately repeated a second and a third time, with a complete disappearance of the symptoms; the prominence between the larynx and the sterno-mastoid no longer existed and the young man was able to swallow with normal ease.

Molinelli's second case was a man fifty-two years of age, who complained of extreme difficulty in swallowing, accompanied by a great deal of anxiety. His symptoms followed directly upon a blow struck in the right anterior and superior part of the neck by a man who had a stone in his fist. Three hours later, the symptoms having persisted, Molinelli employed successfully the same means as in the first instance. In this case there was no prominence in the neck as in the preceding case, and the symptoms were also less intense.

The fourth case, which D'Angers mentions, reported by Dr. Mugna (Annali universali di medicina, Nov. and Dec., 1828), concerned a sexagenarian of "tender and weakened" body who swallowed a large piece of beef tendon which he had not properly masticated, and who, immediately thereafter, had a sensation as though his œsophagus were blocked at the entrance. He felt a continual need of swallowing, but was unable to swallow his saliva or even a drop of liquid. Each moment his anxiety increased.

Called at once, Dr. Mugna found respiration and voice free and no change in the form or appearance of the throat or exterior of the neck. An œsophageal sound was easily passed, crossing the point at which the patient felt the piece of tendon had stopped, but without relief. As the patient indicated the region of the hyoid bone as the seat of the body he felt, Mugna thought of the possibility of dislocation or "diastasis" of the cartilaginous prolongations of the hyoid bone being the cause of the dysphagia. He introduced the index and middle fingers of his right hand into the back of the mouth above the base of the tongue and imparted to the hyoid bone some dis-

placing movements, while he kept his left hand in front of the neck and upon the hyoid bone. This very simple maneuver caused the painful sensation which the patient experienced to disappear immediately, and at once he was able to swallow and drink abundantly.

Two years later Dr. Mugna treated the same patient successfully, in the same manner, for a similar attack.

D'Angers differentiated two ways in which dislocation might occur, one occurring from pressure from the outside and one from pressure from within. The first one corresponds to the dislocation caused by choking as in Molinelli's first case, the second to the dislocation caused by swallowing a large body (Valsalva's case). In the first way he considered the greater cornu to be displaced inwards, its articular facet leaving more or less completely the corresponding facet of the body of the bone. He explains the effect of swallowing a voluminous body as resulting from a lateral and downward movement of the larynx, so that one of its horns engages inside of the corresponding superior horn of the thyroid cartilage, and stays maintained in this position. He thought it conceivable that pressure inwards and downwards upon both greater cornua might cause both cornua to engage in the space between the superior horns of the thyroid cartilage.

Gibb,[3] in 1859, reported a case in a man forty-five years of age, who would feel a sudden click in the left side of his neck which produced a sensation as though something were sticking in his throat. On examination this seemed to depend upon a displacement of the left horn of the hyoid bone, and was generally reduced by throwing the head backwards toward the right side so as to stretch the muscles of the neck and then suddenly depressing the lower jaw, thus putting the depressors of the hyoid bone into operation.

At the patient's death, of pulmonary tuberculosis some years after, Dr. Gibb found "a sort of pouch which answered the purpose of a synovial capsule, and embraced the left thyro-hyoid articulation. It was filled with the clear fluid and had a comparatively large rhomboid sesamoid bone developed in the outer wall and permitted an extraordinary amount of motion."

Dr. Gibb had previously seen three other cases with similar symptoms, all occurring in males, and he thought probably not dependent on such an hydrarthrosis. Later he saw a fifth case in which the patient was a female.

Dr. Ripley,[4] of South Carolina, read, in 1848, before the Parisian Medical Society, a paper on dislocations of the hyoid bone, especially illustrated in his own person, and on the manner of producing them. Dr. Ripley's method of reduction consisted in throwing his head backwards as far as possible so as to place the muscles of his neck on the stretch, and relaxing the lower jaw, at the same time gently pressing or rubbing over the displaced part, "when the displacement became reduced, after a few attempts, with a click."

In 1880 W. H. Daly,[5] of Pittsburgh, reported the case of another physician, Dr. C. D. A., who had been under his treatment. The patient sought relief from a luxation of the left cornu of the hyoid bone which had occurred one-half hour before while laughing. Laryngoscopic examination was negative. The patient's head was bent forward a little to the left side. He complained of dull, pricking pain over the left cornu on straightening his neck. The patient had frequently suffered from similar attacks. His wife was in the habit of cautioning him when laughing or yawning "to take care lest he should put his neck out of joint again!"

The following method of reduction was successful after the third effort: The throat was grasped firmly below the hyoid bone with thumb and index finger of the right hand, the patient's head being steadied with the left. The patient was told to swallow vigorously. As the patient swallowed, Dr. Daley made compression and quick release of the parts between the thumb and finger.

Westmoreland's[6] first case, a policeman, aged 28, while stretching and yawning after breakfast, felt a sudden and severe pain in the side of his neck. He could not close his mouth without pain. "There was a lump over the left side of the neck just over the greater cornu. This appeared to be caused as much by the contraction of the muscles as by the displacement of the cornu." The displacement was apparently upwards and outwards. Laryngoscopic examination revealed no abnormality of either the larynx or pharynx. The patient continually complained of feeling something sticking in his throat.

"The dislocation was easily reduced by having the patient throw his head backward toward the opposite side, rubbing, pressing over the hyoid bone, and at the same time suddenly depressing the lower jaw. It was reduced with a click, audible to everyone in the room, and there was an immediate cessation of all pain."

While the patient had had similar attacks three or four times before, the first time while singing, this last attack was decidedly the worst. He had generally obtained sudden relief by rubbing his throat and moving his head backward and forward, seeking an easy position. He had consulted physicians, but without relief.

Westmoreland's second case, a young traveling salesman, complained of having been in considerable pain for three days; he was unable to keep his mouth closed without increase of pain. Talking also made his suffering worse.

Examination showed a lump over the right side of the hyoid bone, with displacement in the same direction as in the first case but less in degree. The same manipulation to aid reduction was used with success at the first trial, reduction taking place with an audible click.

This patient had also had several attacks. Physicians to whom he had applied for help had invariably prescribed gargles. While gargling with head thrown back and mouth open he would immediately or later get relief in the following peculiar manner. Strangling from fluid running down his throat, he would suddenly bring his head forward to expectorate the medicine. Just at this time he would feel a peculiar jumping sensation in his throat and hear a slight click, and immediately thereupon all unpleasant symptoms would disappear.

To this series of cases may be added a case reported by H. S. Wood[7] in 1890, in which the patient, a subject of advanced pulmonary tuberculosis, suffered a dislocation of his hyoid bone. Dr. Wood hurried to the patient's bedside after receiving a message that the patient had displaced a bone in his neck and was choking.

He found the patient, a man of twenty-seven years, sitting up in bed with head thrown slightly forward, arms crossed over the upper part of his chest, one hand grasping the upper portion of his neck as if to steady his hyoid bone, and the other steadying the larynx. He looked emaciated and distressed. There was slight cyanosis. The patient complained of a sensation of impending suffocation and could not at first be persuaded to let go of his neck. After he had done so, Dr. Wood saw the exact state of affairs. There was a certain degree of prominence on the left side of the neck in the region of the submaxillary triangle. On feeling for the hyoid body, it was found to have deviated from the mesial plane of the neck. As he ran his finger along the greater cornu, the tip of the horn was found to be displaced upward and to the left, so as to be on a level with the angle of the inferior maxilla. No crepitus could be detected. While making the patient swallow, Dr. Wood effected reduction by fixing the thyroid cartilage with one hand and pushing the hyoid cornu in the opposite direction to the displacement. Reduction was accompanied by a perceptible click. The dyspnœa improved directly.

At another time a similar dislocation in the same patient, but with less alarming symptoms, was reduced in the same manner. According to the patient's statement the bone was dislocated during a violent paroxysm of coughing with the head bent to the right side.

In this case there was extensive pulmonary and laryngeal disease. Dr. Wood considered that "owing to the degenerative and ulcerative changes in the neighborhood of the hyoid bone and laryngeal cartilages, the ligaments must have been relaxed with general loss of tonicity in the muscles arising and inserted in the hyoid bone."

Excluding the four cases mentioned by Gibb, in which there is no detailed symptomatology, there remain the eleven cases whose histories I have given in brief. While the symptoms vary somewhat in severity, the resemblance between the cases is so striking that the assumption seems warranted that the underlying cause is the same in each case. This is most probably a dislocation of varying grade of the major cornu of the hyoid bone in the direction outward, or inward and downward. Either type may occur as the result of trauma or of sudden movements of the head, neck, or jaws. In the latter case, it seems likely that there exists a loosened condition of the attachment of the tip of the greater cornu of the hyoid bone to the superior horn of the thyroid cartilage and, perhaps, looseness of the articulation of the cornu with the body of the hyoid, allowing freer play of the tip.

The age of the patients varied from seven years to over sixty. In six of the eleven cases, dislocation took place repeatedly. In four, there is mentioned a definite click as the dislocation was reduced. A prominence in the side of the neck between the inferior ramus of the jaw and the sternomastoid muscle was noted in four cases. There was marked dyspnœa in two cases.

In two cases there was local tuberculosis, namely, of the thyro-hyoid articulation and of the larynx itself.

In the cases examined laryngoscopically no change from the normal could be detected.

It is interesting that three of the eleven cases occurred in physicians. Had they occurred in laymen, it is quite possible that they might never have been diagnosed. Most of the milder cases had frequently consulted physicians without a diagnosis being made. The naturally persistent interest the physicians took in their own cases led eventually to the diagnosis.

Subjectively, the patients experienced pain in swallowing (six cases), total inability to swallow (two cases), marked anxiety (four cases), a feeling as though a foreign body were blocking the œsophagus (three cases). In every case there was immediate and marked relief on reduction of the dislocation.

Four cases came on during sudden movements of the neck and jaws (yawning, coughing, singing, etc.), four as the result of direct trauma from without by choking, or from within through the ingestion of a large solid particle.

There is a surprising similarity in the methods of reduction used successfully in each case.

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NOTES ON NEW BOOKS.

For and Against Experiments on Animals. Evidence Before the Royal Commission on Vivisection. By STEPHEN PAGET, F. R. C. S. $1.50. (*New York: Paul B. Hoeber. 1912.*)

Dr. Paget, who has labored so strenuously in defense of animal experimentation, and who deserves unstinted praise for his work in this line, has prepared here, as he states in the preface, "a clear account of the chief results obtained, during the past thirty years, by the help of experiments on animals." This covers discoveries in physiology, in medicine, in surgery, in the use and effect of drugs in tropical diseases, and in diseases of animals and veterinary surgery. All the progress made is stated by the workers themselves in the evidence given by them before

the Royal Commission on Vivisection. In addition to their statements the case of the antivivisectionists is also presented in the same way—their testimony before the Commission being reported with equal detail. For the work Lord Cromer, President of the Research Defense Society, has written a brief but cogent introduction in defense of experiments on animals and the book as a whole is a most important contribution to the literature on the subect and cannot fail to convince all open-minded readers of its fairness and justice. The cause for experiments on animals should be strengthened the world over by this presentation of the case. Those anxious to inform themselves about this question can find no fairer and more temperate exposition of the *pros* and *cons*. There are many unfortunately who cannot be convinced of the justice of experiments on animals, and nothing can be done to bring these people to see light, but others, who may still be in darkness as to the morality of such procedures, will be illuminated by reading this book which is convincing to any fair-minded individual that it is morally right to use animals for research and the solution of problems dealing with health.

Pharmacology. Action and Uses of Drugs. By Maurice Vejux Tyrode, M. D. Second Edition. $1.50. (*Philadelphia: P. Blakiston's Son & Co., 1912.*)

This work is not intended for the specialist but for students and general practitioners, and both these classes have found it useful. After a brief introduction on "Definitions and General Remarks on the Action of Drugs," the author describes, (1) those "Drugs Whose Constitutional Action is in Greater Prominence"; (2) Ferments, Secretions and Extracts of Animal Organs; (3) "Drugs Whose Local Action is Most in Evidence"; and (4) Drugs of Inorganic Origin. He has accomplished satisfactorily what he undertook to do, and that is to write a pharmacology which should be sufficient for the average man. The publishers have produced a neat book of about 300 pages, but the types used are large and the size of the volume is agreeable.

Pellagra: History, Distribution, Diagnosis, Prognosis, Treatment, Etiology. By Stewart R. Roberts, M. D. Illustrated. $2.50. (*St. Louis: C. V. Mosby Company*, 1912.)

Every new and wide-spread disease calls forth many volumes describing it in various ways, and the literature of pellagra is rapidly growing. Dr. Roberts is an ardent student of this malady, but his gift for writing is not so marked as his industry, and this work shows defects which detract from its value, but many a student and practicing physician will be benefited by reading it, since it covers the ground thoroughly. The style of the author is too fine and aphoristic, and needs tempering. The following sentence is typical; speaking of pellagra the author says, "It is a disease of many symptoms and of many variations; its only consistency is its inconsistency; it seems cured and yet recurs; the pellagrin seems to be approaching his end and yet lives for many years; it spreads and is not contagious; the offspring of the pellagrin receives his mark and yet it is not inheritable; it is not and appears; it is and disappears; it is a morbid entity and yet it contains within itself many lesser morbid entities; it falls with equal right in the sphere of dermatology, neurology and gastrology, and yet it is a general disease; divers diseases become one, and this one is pellagra; there is no pellagra—only the pellagrous." There are certain terms used by the author which are ill-chosen as, for example, "convalescent pellagra," the word convalescent is certainly more correctly applied to the patient than the disease. Again and again he speaks of the neurasthenia or neurasthenic symptoms of the pellagrin. So much obloquy is usually attached to neurasthenia that it seems unkind to the pellagrin to accuse him of showing this, and besides leads to confusion. Dr. Roberts employs the words "dermotagra" and "dermotagrous," which really are the exact equivalents of pellagra and pellagrous, and would apply them simply to the condition of the skin, but this too is unnecessary and confusing, and to have "pellagrous dermotagra" seems redundant to say the least. These are minor defects and we do not mean to lay too much stress upon them. Numerous bibles are famous for misprints and this work is likely to become a classic from one faulty translation. "*Maladie de Saintes Mains*—the sickness of the main saints."

Les Origines de la Trépanation Décompressive. Trépanation néolithique, trépanation pré-Colombienne, trépanation des Kabyles, trépanation traditionelle. Par Le Dr. Lucas Championnière, etc. (*Paris: G. Steinheil, 1912.*)

As the introductory chapter of a large work on trepanning, the author has published this most interesting historical essay separately. Three Frenchmen, Premières, de Baye and Broca, had published earlier works on this subject and in this country Muniz and MacGee wrote a notable book on "Primitive Trephining in Peru" in 1897. But Dr. Championnière, a brilliant surgeon, who has performed many decompressions and written much on this subject, has made a more thorough study of the question than any of his predecessors, and his monograph, with thirty-two illustrations, is the most authoritative work we have. There are certain features connected with the prehistoric skulls, which were trepanned, for which there is no explanation. What were the symptoms which led to the operation? none of the trepanned skulls show any signs of fracture, so it is questionable whether the operation was done to relieve the effects of such injuries. Why were the buttons of bone preserved? for some of these have been found. Trepanning is an interesting phase in the life of prehistoric man about which we can speculate at length, and which is likely never to be satisfactorily explained, but many will find Dr. Championnière's essay both entertaining and instructive.

From the publishers William Green & Sons (Edinburgh and London, 1912) we have received a brief pamphlet entitled, The Local Incidence of Cancer. (Price 1/.) Its author Charles E. Green, F. R. S. E., advances the theory that cancer is due to the consumption of coal, but his evidence seems far from convincing.

Surgical After-Treatment. A Manual of the Conduct of Surgical Convalescence. By L. R. G. Crandon, M. D., and Albert Ehrenfried, M. D. Second Edition. Thoroughly Revised. Illustrated. $6. (*Philadelphia and London: W. B. Saunders Company, 1912.*)

This is an excellent and most useful book and its second edition so soon after the first is most gratifying. For the student and practitioner, who has had but slight hospital experience, the work is invaluable. It is well written and the advice given is sound and practical. The illustrations are well chosen, but it is a pity that many of them are rather hazy, not as sharp-cut as they should be to adorn this otherwise first-rate production.

The Collected Works of Christian Fenger, M.D. Illustrated. Two volumes. $15. (*Philadelphia and London: W. B. Saunders Company, 1912.*)

The friends of Dr. Fenger, as a memorial to him, have had all his papers, with a few exceptions, reprinted in handsome form. Fenger was for many years the leading pathologist and one of the leading surgeons in Chicago, and this tribute is no more than his due. He was one of the brilliant group of physicians in Chicago during the last quarter of the past century and did

much to elevate the standards and ideals of the profession there. His ability was marked, and this collection of papers shows the breadth of his knowledge and interest in his work. He was no surgical specialist, but had trained himself to be a fine general surgeon and his writings cover a broad field, and demonstrate as well the successful qualities of his work, as the fine character of the man.

A Collection of Papers, Published Previous to 1909. By WILLIAM J. MAYO and CHARLES H. MAYO. $10. (*Philadelphia and London: W. B. Saunders Company, 1912.*)

It is now possible for him who wants it to secure practically all that has been written by these two famous brothers. With the addition of these new volumes to those that have recently appeared from the staff of St. Mary's Hospital the writings of the Mayos can be had in book form. How much these volumes will add to their fame is problematical. To-day their clinic is a kind of Mecca, visited by surgeons from all over the world, not only to witness operations by these brilliant men, but also to see how they have organized the best private surgical clinic in the world.

But there will be readers who will enjoy studying these volumes to note the evolution of the ideas and practices of the Mayos and from this point of view the volumes will be most instructive and valuable. They are splendid evidence of the constant activity, thoughtfulness and broad interest of these most remarkable men, who in their joint work, remind one somewhat of the Wright brothers, devoted to each other, and working with the highest of principles.

Collected Papers by the Staff of St. Mary's Hospital. Mayo Clinic, Rochester, Minnesota, 1911. $5.50. (*Philadelphia and London: W. B. Saunders Company, 1912.*)

In this volume are all of the papers read or published by any member of the staff of the hospital during the year 1911. Some of these have already appeared in the medical journals, others will appear later. There are twenty-three contributors with nineteen papers on the alimentary canal, one on hernia, sixteen on genito-urinary questions, four on ductless glands, three on the thorax and its extremities, three on technic, and seven general papers. The volume has a good index, and some of the papers are well illustrated. The staff of the Mayo Clinic has now become so large that, although much more work is being turned out now than earlier, it is losing the very distinctive and interesting character it had when the Mayo brothers were to all intents and purposes the staff. They have now associated many workers with them and as a necessary result the work produced is uneven, and lacks the mark of genius exhibited by the founders of this extraordinary clinic.

An Essay on Hasheesh. Including Observations and Experiments. By VICTOR ROBINSON, Pharmaceutical Chemist, Columbia University. 50 cts. (*New York: Medical Review of Reviews, 1912.*)

After experimenting on himself and some of his friends with this drug, the author has written a brief essay relating his own experiences as well as those of his friends. He introduces his essay with a brief account of the drug in history and medicine. Mr. Robinson has not hesitated to give the names of those he experimented upon, which, as all he tells of them is not pleasant, indicates a certain lack of delicacy on his part, and leaves a disagreeable and unsatisfactory impression of his work, which is doubtless intended seriously, but seems lacking in true scientific spirit. The essay is brief and is unimportant as adding anything new to our knowledge of hasheesh and its effects.

What To Do in Cases of Poisoning. By WILLIAM MURRELL, M. D., F. R. C. P., etc. Eleventh Edition. $1. (*New York: Paul B. Hoeber, 1912.*)

This guide has been popular for many years in England, and may well become so in this country, but in another edition should be carefully revised, so as to eliminate some poisons (plants and quack remedies) used abroad that are unknown here, and others met with here inserted in their place. It is a very small volume that a practitioner who carries a bag can always have at hand to use in an obscure case, and the advice contained is good. All the poisons are arranged alphabetically so it is easy to look up their symptoms and antidotes.

The Care of the Skin in Health. By W. ALLAN JAMIESON, M. D., F. R. C. P. (Eng.). $1. (*London: Henry Frowde and Hodder & Stoughton, 1912.*)

This is a very brief essay intended for the laity, and as such can be recommended with safety, for it is simply and clearly written and none could go astray in following the author's advice. The only objection to it is its cost, for it could be widely distributed with benefit among the intelligent poor if only its expense were reduced, as could easily have been done.

Sexual Impotence. By VICTOR G. VECKI, M. D. Fourth Edition. Enlarged. $2.25. (*Philadelphia and London: W. B. Saunders Company, 1912.*)

For the general practitioner this book may serve its purpose, but for the profounder student of the subject it lacks real scientific value. Its importance was not so great as to make it worthwhile to reprint the book.

Franklin's Contribution to Medicine. By THEODORE DILLER. $2. (*Brooklyn, New York: Albert T. Huntington, 1912.*)

In a neatly printed volume Dr. Diller has collected the writings of Franklin which deal with medical questions; almost all he wrote on the subject is to be found in letters addressed to many correspondents, and here, for the first time in English, Franklin's views on this science have been brought together. This makes the essay an important contribution to medical history. That Franklin took a lively interest in medicine is not strange, for he had a mind of exceptional breadth, and always had a desire to be well informed on all scientific questions and associated himself with the most intelligent men in America and Europe. Philadelphians, especially, but all Americans owe him a debt of gratitude for his efforts in founding the first medical school in America; that it was born is largely due to him. Franklin's views on hygiene were exceptionally sound for his time, and all physicians will be glad to acquaint themselves with his ideas on this branch as well as others related to medicine.

Children: Their Care and Management. By E. M. BROCKBANK, M. D. (Vict.), F. R. C. P. $1.50. (*London: Henry Frowde and Hodder & Stoughton, 1912.*)

There are numberless books on this subject, but the numbers of young mothers and nurses is constantly growing, so that there are always readers for a new book of this kind; and many a young doctor will find it useful also. It deals with infants and children up to the age of eight or ten; and takes up all the essential points that should be carefully considered in their upbringing, such as nursing, washing, clothes, diet, environment, etc. In no way does it lead mothers or nurses to intrude upon the proper province of the doctor, in which respect many of the books on this subject err, and while the advice given on many

points seems rather cursory, it is sufficient for all intents and purposes. The book contains good counsel and compares favorably with the majority of similar works.

The Surgical Clinics of John B. Murphy, M. D. June, 1912, Vol. I, Nos. 3 & 4. $8 per year. Bi-monthly. (*Philadelphia and London: W. B. Saunders Company.*)

There is a vividness about these Clinics which portrays well the nature of Dr. Murphy, and the excellent quality of his work. The method of presentation will doubtless add to the popularity of these talks at the operating table. Many different surgical questions are discussed in these numbers, and if read with care a student will get valuable hints from them.

Studies in Cancer and Allied Subjects: Pathology. Conducted Under the George Crocker Special Research Fund at Columbia University. Vol. II. (*New York: The Columbia University Press, 1912.*)

This volume opens with a brief but adequate introduction by Dr. MacCallum, who sets forth clearly the difficulties inherent to the solution of the cause of cancer. This is followed by a series of twenty-seven papers by Levin, Siltenfield, Lambert, Hanes, Frank, and Unger. Some are the combined work of Levin and Siltenfield, Lambert and Hanes, and Frank and Unger, but a majority are written by Levin and Lambert alone. All these papers have appeared elsewhere, but as the product of work done with the aid of this fund it is well to have them collected in this form. Some of them are little more than very brief preliminary notes, of only a page or less in length. There are a number of beautiful illustrations, and as a piece of press work the volume deserves commendation, though we question the need and, if not needful, the righteousness of publishing so costly a volume at the expense of the fund. Several other volumes dealing with the cancer problem are in preparation, and there is no doubt that the series will form a most important contribution in the elucidation of the problem. The work done already by the men mentioned augurs well for what is to follow, and the report is one which all students of this and allied problems must have at hand.

The Mechanistic Conception of Life: Biological Essays. By Jacques Loeb, M. D., etc. $1.50. (*Chicago, Illinois: The University of Chicago Press, 1912.*)

The author, known to scientists as a most brilliant and original worker along certain lines, has unfortunately to the public, if it knows him at all, a sensational newspaper notoriety because of some of his early investigations into artificial parthenogenesis. It is to be hoped, however, that these essays may make him better known to serious readers that they may learn what a profound thinker and extraordinary investigator Jacques Loeb is. These cannot be called "popular" essays, but with little trouble their essential meaning can be grasped by careful reading, and they cannot fail to stimulate the student's interest. They have already appeared elsewhere in various publications, so that there is necessarily some repetition of facts in this volume, but some of the problems discussed by the author are better for this repetition, as they are not at first reading always easy to comprehend. This volume may be called "entrancing"; and all eager to know more of the origin of life will find no modern book of its size nearly so instructive, or inspiring.

Practical Anatomy. By John C. Heisler, M. D. $4.50. (*Philadelphia and London: J. B. Lippincott Company, 1912.*)

Bound in flexible covers this anatomy is certainly practical for a laboratory worker, but why should the term "practical anatomy" be used any longer, since all anatomy is practical if applied to a definite end? Dr. Heisler's book is sufficiently illustrated and well printed, but the reason he gives in his preface for not using the more advanced nomenclature [B. N. A.] does not seem to us to carry much weight. If those, like himself, who believe in it will not use it, then it will never become universally adopted; why it will be easier to adopt the nomenclature later rather than now is not evident. Points of special clinical interest concerning structures under discussion are introduced in smaller type. This is done to hold the interest of the student. It does not seem that this is a very wise procedure; such points are multifold, and no two authors would agree as to which had better be inserted or omitted. The result is a product like the majority of illustrated medical dictionaries; the illustrations are chosen quite hap-hazard, and add little or no value to the work. The author takes up in sequence the upper limb, the lower limb, the head and neck, and the abdomen and thorax, and for the student who wishes to get through his anatomy without the labor required to master Gray's classic, this anatomy will serve well.

Oxford Medical Publications: Gonococcal Infections. By Major C. E. Pollock and Major L. W. Harrison. $2. (*London: Henry Frowde and Hodder & Stoughton, 1912.*)

The authors, both of whom belong to the Royal Army Medical Corps, have written a small and simple book, which is, however, hardly sufficient for even the general practitioner. After discussing the pathology of the gonococcal infections, they consider both vaccine and serum therapy for these, and then describe the infections in men, women, and children and the proper treatment for each. The work concludes with a very brief chapter on gonococcal septicæmia. Only a superficial knowledge of the troubles which are due to an infection with the gonococcus can be derived from a reading of this publication.

Die physikalische Therapie der Gelenkkrankheiten für Aerzte und Studirende. Von Dr. Eduard Weisz. $1.50. (*Berlin and Wien: Urban & Schwarzenberg; New York: Rebman Company, 1912.*)

This treatise on the treatment of diseases of the joints is divided into two parts—a general and a special. In the first the author takes up all the various physical methods and describes their proper employment, while in the special part he discusses more fully their practical application to congenital joint troubles, neoplasms, joint neuroses and traumas, bacterial joint infections, and diseases of the joints due to metabolic disturbances. It is a serviceable work to any student who reads German easily, although it deals but slightly with operative procedures, but the value of rest, extension, light, electricity, hyperæmia and many other measures is well shown. It is a useful small manual for the general practitioner rather than the specialist.

A System of Treatment. In Four Volumes. Edited by Arthur Latham and T. Crisp English. (*New York: The Macmillan Company, 1912.*)

There has been almost an epidemic of publication of exhaustive treatises on therapeutics, and several large works have come out in the last year or two. The writers of this one are on the staff of St. George's Hospital, London, an institution from which much excellent work has come. This system has two peculiarities which arrest the attention at once; the four volumes appear simultaneously and each volume has a complete index to the whole work. Another point worthy of mention is the success of the bookmaker's art. Each of these volumes contains over four-

teen hundred pages and yet they are of convenient size and weight. It does seem as if American publishers might learn a little in this regard from their brethren abroad and give us books which are less cumbersome to handle.

It is impossible for one reviewer to discuss such a work in detail, particularly as it includes medicine, surgery, tropical diseases, dermatology, diseases of the eye, obstetrics and gynecology, not to speak of other subjects. The general impression is that the work as a whole is most satisfactory. The discussion of treatment is usually complete and according to the best modern standards. The editors have made the effort to include the most recent advances which are worthy of notice. There are many general articles which add to the value of the work, as for example on the management of the sick room, surgical technique, shock, poisons and antidotes, etc. Treatment by vaccines receives a considerable amount of attention. It may be said that one can find information on practically any question concerned with therapy.

The editors comment on the difficulty of arrangement and they have doubtless solved their troubles in the best way possible. However, it is difficult to see why acute abscess and whitlow are put under infective diseases. Again, why should tuberculosis be divided and discussed here and there? Why is acute tuberculosis under the infective diseases and pulmonary tuberculosis under diseases of the lungs with tuberculous meningitis in a separate section? Would it not have been better to bring together the whole discussion of tuberculosis in one section? The same comment applies to syphilis. Certain infections are considered quite apart under the heading of Tropical Fevers; malaria, Malta fever and plague are among these. Under the heading of Abdominal Tropical Diseases we have cholera and dysentery among others. These diseases are by no means confined to the tropics and this seems an artificial arrangement. However, it must be said that the complete index in each volume renders it easy to find the reference to a particular disease. Those who have struggled with the difficulties of classification will be ready to sympathise with the editors in the attempt to do the best with this question.

As is natural the articles vary greatly in fullness and value, for the editors of such a work have great difficulty in securing even a degree of uniformity. Take for example the section on nephritis. The discussion of the medical treatment of chronic interstitial nephritis occupies a little more than a page, while the surgical treatment of nephritis occupies nearly double the space. Surely this is not a proper disposal of space. It is a pleasure to turn to the discussion of appendicitis, for the article is a splendid one by the surgical editor (Mr. English), and in it the attitude towards early operation is to be highly commended. Attention is drawn to this as the writer has recently gone over this question in some English and German works in which the opinions expressed deserved strong condemnation. It is to be hoped that this section will be widely read, digested, and acted upon in practice.

It is not to be expected that any reviewer would agree with every part of such a work and if he is looking for opinions to disagree with there is no difficulty in finding them. However, there are some points which are deserving of mention. Under typhoid fever, constipation is given as a sign that milk is not agreeing. It would be interesting to know the reasons for this; most of us would take exactly a contrary view. The view that carbohydrates should be withheld is also against the general opinion. The use of the tub bath is discussed as an antipyretic measure. This mistaken idea dies hard and it is a pity that the editors did not correct it. We meet an old friend, the Woodbridge treatment, and one hardly knows whether to laugh or weep. The editors certainly nodded here. We fail to find any mention of the use of hexamethylenamin in typhoid fever, which is a serious omission. The article on diabetes mellitus is a very satisfactory one, especially in its clear and specific directions. James Mackenzie contributes an excellent discussion on the treatment of cardiac conditions with an especially clear exposition of the general principles of therapy in this domain. A suggestion which may be made is that a fuller discussion of the value of strophanthin given intramuscularly would be an advantage. This is one of the greatest additions to cardiac therapy of recent years.

The first and second volumes discuss general medical and surgical treatment. Surgical measures are fully taken up and the articles are well illustrated. As a matter of interest the subject of mucous colitis was selected for comment. Some space is given to the surgical treatment and it is interesting to find what the writer considers mucous colitis to be. He apparently limits the term to cases in which there is an inflammatory condition present. As the term is generally used in this country such a finding would exclude the diagnosis of mucous colitis. As the author does not believe in a mucous colitis secondary to a general nervous condition, it is evident that his views have to be carefully understood before his article has any value to the reader. In the discussion of the treatment of diseases of the nervous system, the editors have been fortunate in securing a brilliant list of contributors and these sections are excellent throughout. One name is persistently misspelled, that of the man who described the re-education exercises so useful in tabes; this appears as Fraenkel instead of Frenkel.

The third volume deals with special subjects; many therapeutic methods, including vaccine and serum therapy, are discussed, and tropical diseases, those of the eye, nose, throat, and skin diseases are included. The fourth volume deals with obstetrics and gynecology.

This system should prove especially useful for the general practitioner as he can find information on any subject. The full index adds greatly to its value. Altogether we can cordially recommend it and congratulate the editors on their success.

Diagnose der Simulation nervöser Symptome. Ein Lehrbuch für den Praktiker. Von PRIV.-DOZ. DR. SIEGMUND ERBEN, Wein. $2.15. (*Berlin and Wien: Urban & Schwarzenberg; New York: Rebman Company, 1912.*)

This is a valuable work on the differential diagnosis of organic nervous troubles and simulated nervous symptoms. To decide whether a symptom is really of organic origin, or purely functional is oftentimes one of the most difficult tasks that the physician can perform—an exact determination cannot frequently be arrived at. It is often said "time alone can tell," but this is not absolutely true, for though a symptom apparently functional in nature may disappear after a longer or shorter interval, there is no final proof that it was not due to some real organic lesion. In fact the more we learn of disturbances of the human system, the less becomes the number of conditions which can rightly be classified as functional. In medico-legal cases arising from accidents the question of the simulation of the symptoms is frequently the cause of much divergence of opinion among experts, and this careful study of Dr. Erben's will help the general practitioner from falling into avoidable errors. He begins with a study of nervousness, neurasthenia, and the neuroses of accidents and their various forms of expression in different organs, and in a similar way discusses anæsthesia, hypæsthesia, paræsthesia, pain, hyperæsthesia, motor symptoms, dizziness, sensation of illness, attacks of unconsciousness, epilepsy, hysteria, coma, and insanity. The monograph forms an important addition to the study of nervous diseases, and also to psychiatry, for after all if a symptom is simulated it is above all essential that the mental condition of the patient should be studied.

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